ANALOGS OF LYSOPHOSPHATIDIC ACID AND METHODS OF MAKING AND USING THEREOF

ACKNOWLEDGEMENTS

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CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. provisional application Serial No. 60/462,095, filed April 9, 2003. This application is hereby incorporated by this reference in its entirety for all of its teachings.

BACKGROUND

Lysophosphatidic acid (1- or 2-*O*-acyl-*sn*-glycero-3-phosphate, *sn*-1 or *sn*-2 LPA), a simple phospholipid, is an intercellular signaling molecule with a variety of biologic effects [1]. LPA induces cell proliferation, morphological changes, and has been shown to be involved in many physiological and pathological processes including neurogenesis [2], myelination, angiogenesis [3], wound healing [4], and cancer progression [5].

Normally, LPA is present in serum at low levels and is not detectable in platelet-poor plasma, whole blood, or cerebrospinal fluid. LPA is present at elevated levels, however, in the ascites of ovarian cancer patients and may thus contribute to the progression of human cancer [6]. Interestingly, LPA produced by stimulated platelets is chemically distinct from that found in ascites of ovarian cancer patients. *sn*-1 LPA is preferentially produced in platelets, whereas *sn*-2 type is found to be predominant in ascites. Therefore, levels of *sn*-2 LPA seem to be associated with the initiation and progression of ovarian cancer [7]. On the other hand, it has been demonstrated that *sn*-2 LPA is not stable under physiological conditions; it is rapidly converted to *sn*-1 LPA and vis versa as a result of intramolecular acyl chain

migration. This reaction, facilitated by acidic and basic conditions, yields an equilibrium mixture of 1-acyl and 2-acyl-*sn*-glycerol-3-phosphate favoring the 1-acyl isomer. The instability of 2-acyl-*sn*-glycerol-3-phosphate is therefore a challenge against isolation and structure-activity studies of individual LPA species.

Although three mammalian genes, Edg-2/LPA_1, Edg-4/LPA_2, and Edg-7/LPA_3 encoding high-affinity LPA receptors have been cloned and characterized [8], the function of particular receptors in the mammalian system and the molecular mechanism of LPA actions have not been elucidated [9]. Among the reasons for this ignorance is the lack of molecular tools, especially the metabolically stable and selective ligands for LPA receptors [10]. Described herein are LPA analogs with improved stability and/or with receptor-selective activity. One approach is to produce and investigate acylic analogs of LPA. Another approach involves the preparation and analysis of cyclic analogs of LPA. Although cyclic compounds are known[11-19], the cyclic as well as acyclic analogs described herein possess improved metabolic stability and biological activity.

SUMMARY

Described herein are analogs of lysophosphatidic acid. Also described herein are methods of making and using analogs of lysophosphatidic acid.

The advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the aspects described below. The advantages described below will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several aspects described below. Like numbers represent the same elements throughout the figures.

Figure 1 shows a reaction scheme for producing a diol having the formula III.

Figure 2 shows a reaction scheme for converting a diol having the formula III to other derivatives.

Figure 3 shows a reaction scheme for producing α,α-difluoro compounds described herein.

Figure 4 shows a reaction scheme for producing α,α-difluoro compounds described herein.

Figure 5 shows a reaction scheme for producing difluoro compounds described herein.

Figure 6 shows a reaction scheme for producing hydroxyethoxy compounds described herein.

Figure 7 shows a reaction scheme for producing hydroxyethoxy compounds described herein.

Figure 8 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 9 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 10 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 11 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 12 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 13 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 14 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 15 shows a reaction scheme for producing α-monofluoro compounds described herein.

Figure 16 shows the structures of selected known analogs of LPA described herein.

Figure 17 shows a reaction scheme for producing cyclic analogs of LPA described herein.

Figure 18 shows a proposed reaction scheme for producing cyclic analogs of LPA described herein.

Figure 19 shows a proposed reaction scheme for producing cyclic analogs of LPA described herein.

Figure 20 shows a proposed reaction scheme for producing cyclic analogs of LPA described herein.

Figure 21 shows a reaction scheme for producing cyclic analogs of LPA described herein.

Figure 22 shows a reaction scheme for producing cyclic analogs of LPA described herein.

DETAILED DESCRIPTION

Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that the aspects described below are not limited to specific compounds, synthetic methods, or uses as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting.

In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings:

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

"Optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not. For example, the phrase "optionally substituted lower alkyl" means that the lower alkyl group can or can not be substituted and that the description includes both unsubstituted lower alkyl and lower alkyl where there is substitution.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

References in the specification and concluding claims to parts by weight, of a particular element or component in a composition or article, denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed.

Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

A weight percent of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

Variables such as R^1, R^2, R^3, R^6, R^7, X^1, X^2, Y^1, Y^2, U, V, W, and Z used throughout the application are the same variables as previously defined unless stated to the contrary.

The term "substantially" with respect to the stereochemistry at carbon a refers to greater than 95%, greater than 97%, greater than 98%, greater than 99%, greater than 99.5%, or 100% of one enantiomer with respect to the other enantiomer. The terms "R" and "S" with respect to the stereochemistry at carbon a are also referred to in the art as "D" and "L," respectively.

The term "alkyl group" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 25 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, pentyl, hexyl, heptyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like. Examples of longer chain alkyl groups include, but are not limited to, an oleate group or a palmitate group. A "lower alkyl" group is an alkyl group containing from one to six carbon atoms.

The term "cycloalkyl group" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. The term "heterocycloalkyl group" is a cycloalkyl group as defined above where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulphur, or phosphorus.

The term "aryl group" as used herein is any carbon-based aromatic group including, but not limited to, benzene, naphthalene, etc. The term "aromatic" also

includes "heteroaryl group," which is defined as an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, alkynyl, alkenyl, aryl, halide, nitro, amino, ester, ketone, aldehyde, hydroxy, carboxylic acid, or alkoxy.

The term "silyl group" as used herein is represented by the formula -SiRR'R", where R, R', and R" can be, independently, hydrogen, an alkyl, aryl, cycloalkyl, halogenated alkyl, alkoxy, or heterocycloalkyl group described above.

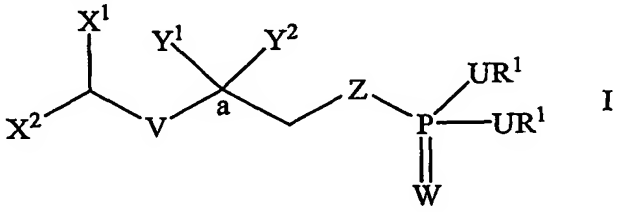
The term "protecting group" as used herein is a group that can be chemically bound to an oxygen atom, and subsequently removed (either chemically, *in-vitro*, or *in-vivo*) from the oxygen atom by predictable methods. Examples of many of the possible protective groups can be found in *Protective Groups in Organic Synthesis* by T.W. Green, John Wiley and Sons, 1981, which is incorporated herein by reference in its entirety.

The term "cationic counterion" as used herein is any ion bearing a positive charge. The cationic counterion can be mono- or multivalent.

I. Analogs of LPA

a. Acylic Compounds

In one aspect described herein is a compound having the formula I



I

wherein

X^1, X^2, Y^1, and Y^2 comprises, independently, hydrogen, fluorine, a hydroxyl group, a branched or straight chain C_1 to C_{25} alkyl group, OR^2, $OCH_2CH_2OR^2$, $OC(O)R^3$, or $NC(O)R^3$;

each U comprises, independently, oxygen, sulfur, or NR^1;

V is not present or when V is present, V comprises oxygen or sulfur;

W comprises oxygen or sulfur;

Z comprises oxygen, sulfur, NR^1, CH_2, CHF, CF_2, or $CHOR^2$;

each R^1 comprises, independently, hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cationic counterion, or both R^1 form a cyclic or heterocyclic group;

R^2 comprises hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group or a protecting group;

R^3 comprises a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group,

or the pharmaceutically acceptable salt or ester thereof,

wherein when Y^1 and Y^2 are different groups, the stereochemistry at carbon a is either substantially R or substantially S, and

wherein the compound having the formula I is not 1-acyl-*sn*-glycerol 3-phosphate and 2-acyl-*sn*-glycerol 3-phosphate.

The compounds 1-acyl-*sn*-glycerol 3-phosphate and 2-acyl-*sn*-glycerol 3-phosphate are generally referred to as lysophosphatidic acid (LPA).

In one aspect, both of R^1 can be part of a cyclo or heterocyclo group. For example, the heterocyclic group can be morpholino, piperidino, etc.

In one aspect, compounds having the formula I are monofluoro compounds. In one aspect, each U comprises oxygen, W is oxygen, V is not present, X^1 is hydrogen, and X^2 is fluorine. In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, X^1 is hydrogen, and X^2 is fluorine. In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, X^1 is hydrogen, X^2 is fluorine, Y^1 is hydrogen, and Y^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and R^1 is hydrogen. In another aspect, Z is oxygen, X^1 is hydrogen, X^2 is fluorine, Y^1 is hydrogen, and Y^2 is

$OC(O)R^3$, wherein R^3 is an oleate group or a palmitate group, and R^1 is hydrogen, and the stereochemistry at carbon a is R or S.

In another aspect, the monofluoro compound is a compound having the formula I, wherein each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, Y^1 is hydrogen, and Y^2 is fluorine. In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, Y^1 is hydrogen, Y^2 is fluorine, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and each R^1 is hydrogen. In a further aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, Y^1 is hydrogen, Y^2 is fluorine, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is an oleate group or a palmitate group, wherein the stereochemistry at carbon a is R or S.

In another aspect, the monofluoro compound is a compound having the formula I, wherein each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, Y^2 is a hydroxyl group. In one aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, Y^2 is a hydroxyl group, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and each R^1 is hydrogen. In one aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, Y^2 is a hydroxyl group, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is an oleate group or a palmitate group, and each R^1 is hydrogen, wherein the stereochemistry at carbon a is R or S.

In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, and Y^2 is a hydroxyl group. In one aspect, each U comprises oxygen, W is oxygen, V is not present, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and each R^1 is ethyl. In a further aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, Y^2 is a hydroxyl group, X^1 is hydrogen, X^2 is a silyl group or an alkyl group, and each R^1 is ethyl.

In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, and Y^2 is an alkyl group. In one aspect, each U comprises

oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, Y^2 is a hydroxyl group, X^1 is hydrogen, X^2 is a silyl group, a hydroxyl group, or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and each R^1 is ethyl or each R^1 is hydrogen.

In a further aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, and Y^2 is a hydroxyl group. In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CHF, Y^1 is hydrogen, Y^2 is a hydroxyl group, X^1 is hydrogen, X^2 is an alkyl group, and each R^1 is ethyl or each R^1 is hydrogen.

Methods for preparing monofluoro compounds having the formula I are presented below.

In another aspect, the compound having the formula I is a difluoro compound, wherein Z is CF_2. In one aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CF_2, Y^1 is hydrogen, Y^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and each R^1 is an ethyl group or a sodium ion. In one aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CF_2, Y^1 is hydrogen, Y^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, each R^1 is an ethyl group or a sodium ion, X^1 is hydrogen and X^2 is OH or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, wherein the stereochemistry at carbon a is R or S.

In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CF_2, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, and each R^1 is an ethyl group or a sodium ion. In a further aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CF_2, X^1 is hydrogen, X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, each R^1 is an ethyl group or a sodium ion, Y^1 is hydrogen and Y^2 is OH or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, wherein the stereochemistry at carbon a is R or S.

In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z

is CF_2, X^1 is hydrogen, X^2 is OH, Y^1 is hydrogen, Y^2 is OH, and each R^1 is an ethyl group.

Methods for preparing difluoro compounds having the formula I where Z is CF_2 are described below in the Examples section.

In another aspect, the compounds having the formula I are difluoro compounds, wherein each U comprises oxygen, W is oxygen, V is not present, Z is CH_2 and X^1 and X^2 are fluorine. In one aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CH_2, X^1 and X^2 are fluorine, Y^1 is hydrogen, Y^2 is a hydroxyl group, OR^2, or $OC(O)R^3$. In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is CH_2, X^1 and X^2 are fluorine, Y^1 is hydrogen, Y^2 is a hydroxyl group, OR^2, or $OC(O)R^3$, and each R^1 is hydrogen or a methyl group, wherein the stereochemistry at carbon a is R or S.

Methods for preparing difluoro compounds having the formula I where Z is CH_2 and X^1 and X^2 are fluorine are described in the Examples section below.

In another aspect, the compounds having the formula I are nonfluoro compounds. In one aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, Y^1 is hydrogen, and Y^2 is $OCH_2CH_2OR^2$, wherein R^2 is hydrogen or a protecting group. In another aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, Y^1 is hydrogen, Y^2 is $OCH_2CH_2OR^2$, wherein R^2 is hydrogen or a protecting group, X^1 is hydrogen, and X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, Y^1 is hydrogen, Y^2 is $OCH_2CH_2OR^2$, wherein R^2 is hydrogen or a protecting group, X^1 is hydrogen, and X^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, each R^1 is a methyl group or hydrogen, and the stereochemistry at carbon a is R or S.

In another aspect, the compounds having the formula I are nonfluoro compounds, wherein each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, X^1 is hydrogen and X^2 is $OCH_2CH_2OR^2$, wherein R^2 is hydrogen or a protecting group. In one aspect, each U comprises oxygen, each U comprises oxygen,

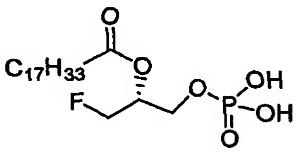
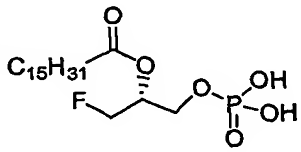
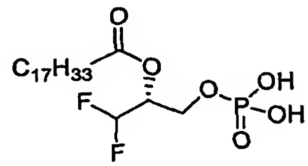
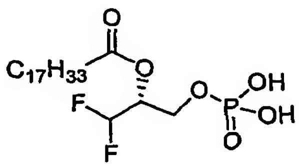
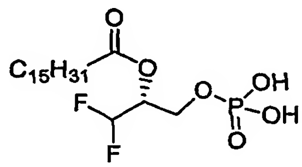
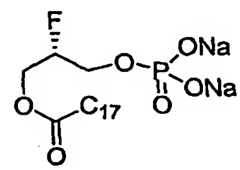
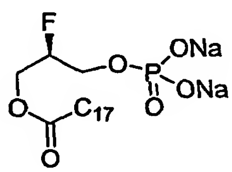
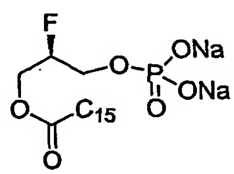
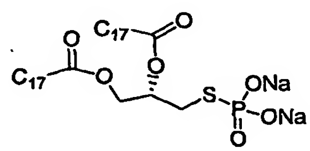
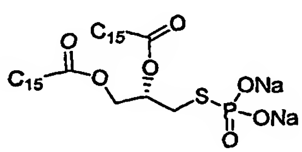
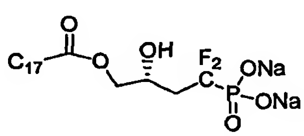
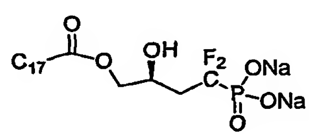
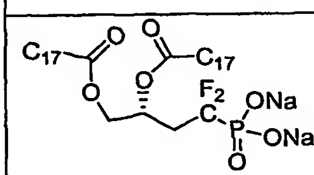
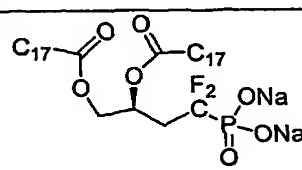
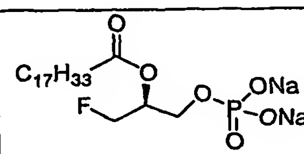
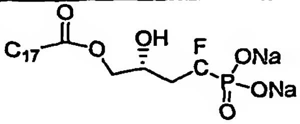
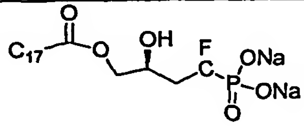
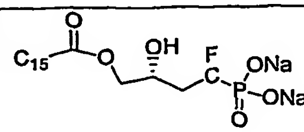
W is oxygen, V is not present, Z is oxygen, X^1 is hydrogen, X^2 is $OCH_2CH_2OR^2$, wherein R^2 is hydrogen or a protecting group, Y^1 is hydrogen, and Y^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, each U comprises oxygen, W is oxygen, V is not present, Z is oxygen, X^1 is hydrogen, X^2 is $OCH_2CH_2OR^2$, wherein R^2 is hydrogen or a protecting group, Y^1 is hydrogen, and Y^2 is $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group, each R^1 is a methyl group or hydrogen, and the stereochemistry at carbon a is R or S.

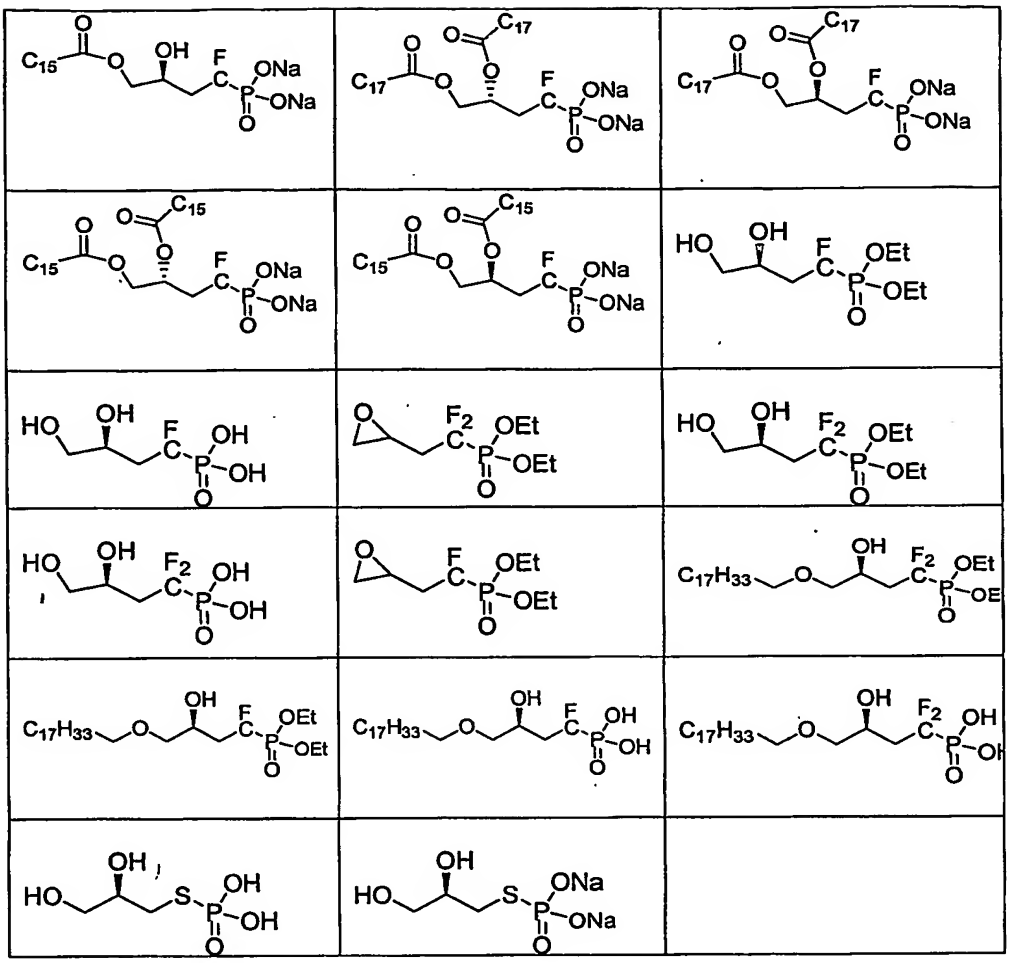
Methods for preparing nonfluoro compounds having the formula I discussed above are described below in the Examples section.

In one aspect, when V is not present in formula I, each U comprises oxygen, W is oxygen, X^1 and Y^1 are hydrogen, and X^2 is hydroxyl, then Y^2 is not hydroxyl.

In one embodiment, the compounds having the formula I are presented in Table 1 below.

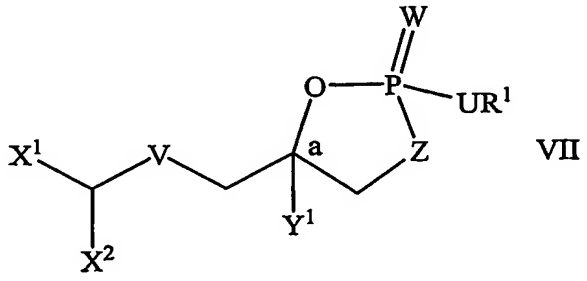
TABLE 1



b. Cyclic Compounds

In one embodiment, described herein are compounds having the formula VII



VII

wherein

X^1, X^2, and Y^1 comprises, independently, hydrogen, fluorine, a hydroxyl group, a branched or straight chain C_1 to C_{25} alkyl group, OR^2, $OCH_2CH_2OR^2$, $OC(O)R^3$, or $NC(O)R^3$;

U comprises oxygen, sulfur, or NR^1;

V is not present or when V is present, V comprises oxygen or sulfur;

W comprises oxygen or sulfur;

Z comprises oxygen, sulfur, NR^1, CH_2, CHF, CF_2, or $CHOR^2$;

each R^1 comprises hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, or a cationic counterion;

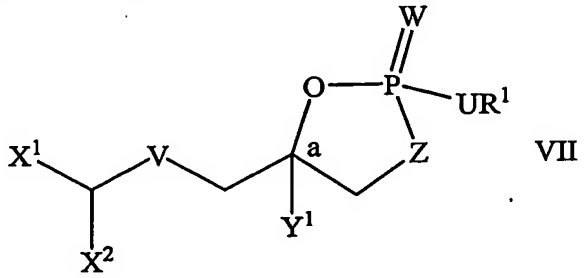
R^2 comprises hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group or a protecting group;

R^3 comprises a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group;

or the pharmaceutically acceptable salt or ester thereof,

wherein the stereochemistry at carbon a is either substantially R or substantially S, wherein when W is oxygen, V is not present, X^1 and Y^1 are hydrogen, and X^2 is $OC(O)R^3$, then Z is not CH_2 or oxygen.

In another aspect, described herein are compounds having the formula VII



VII

wherein

X^1, X^2, and Y^1 comprises, independently, hydrogen, fluorine, a hydroxyl group, a branched or straight chain C_1 to C_{25} alkyl group, OR^2, $OCH_2CH_2OR^2$, $OC(O)R^3$, or $NC(O)R^3$;

U comprises oxygen, sulfur, or NR^1;

V is not present or when V is present, V comprises oxygen or sulfur;

W comprises oxygen or sulfur;

Z comprises sulfur, NR^1, CHF, CF_2, or $CHOR^2$;

Each R^1 comprises hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, or a cationic counterion;

R^2 comprises hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group or a protecting group;

R^3 comprises a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group; an aryl group, a heteroaryl group;

or the pharmaceutically acceptable salt or ester thereof,

wherein the stereochemistry at carbon a is either substantially R or substantially S.

In one aspect, when the compound has the formula VII, U comprises oxygen, Y^1 is hydrogen and Z is CHF, CF_2, or CH_2. In another embodiment, U comprises oxygen, Y^1 is hydrogen, Z is CHF, and W is oxygen. In a further embodiment, U comprises oxygen, Y^1 is hydrogen, Z is CHF, W is oxygen, V is not present, and R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In another embodiment, U comprises oxygen, Y^1 is hydrogen, Z is CHF, W is oxygen, V is not present, R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen and X^2 is OH or $OC(O)R^3$, wherein R^3 comprises a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

In one aspect, when the compound has the formula VII, U comprises oxygen, Z is CF_2 and W is oxygen. In another aspect, U comprises oxygen, Z is CF_2, W is oxygen, V is not present, and R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, U comprises oxygen, Z is CF_2, W is oxygen, V is not present, R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen, and X^2 is OH or $OC(O)R^3$, wherein R^3 is a branched

or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

In one aspect, when the compound has the formula VII, U comprises oxygen, Z is CHF or CF_2 and W is oxygen. In another aspect, U comprises oxygen, Z is CHF or CF_2, W is oxygen, V is oxygen, and R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, U comprises oxygen, Z is CHF or CF_2, W is oxygen, V is oxygen, R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen, and X^2 is OH or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

In one aspect, when the compound has the formula VII, U comprises oxygen, Z is CH_2 and W is oxygen. In another aspect, U comprises oxygen, Z is CH_2, W is oxygen, V is not present, and R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, U comprises oxygen, Z is CH_2, W is oxygen, V is not present, R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen, and X^2 is OH or $OC(O)R^3$, wherein R^3 comprises a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

In one aspect, when the compound has the formula VII, U comprises oxygen, Z is CH_2, W is oxygen, V is oxygen, and R^1 comprises hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In another aspect, U comprises oxygen, X^1 is hydrogen and X^2 is a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

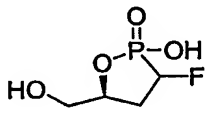
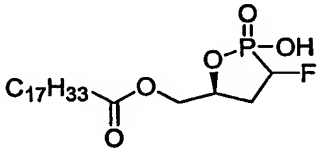
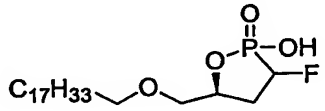
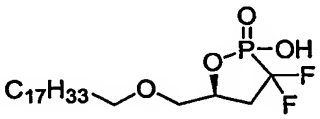
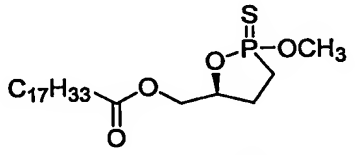
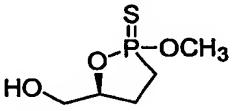
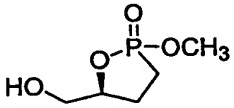
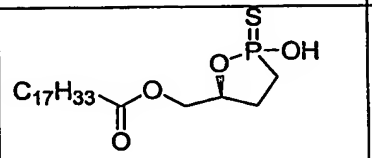
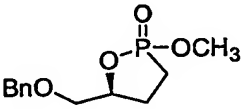
In one aspect, when the compound has the formula VII, U comprises oxygen, Z is CH_2 and W is sulfur. In another aspect, U comprises oxygen, Z is CH_2, W is sulfur, V is not present, and R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, U comprises oxygen, Z is CH_2, W is sulfur, V is not present, and R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen, and X^2 is OH or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

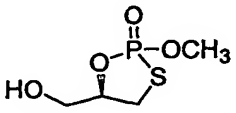
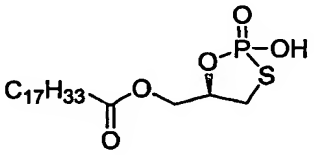
In one aspect, when the compound has the formula VII, U comprises oxygen, Z is sulfur and W is oxygen. In another aspect, U comprises oxygen, Z is sulfur, W is oxygen, V is not present, and R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, U comprises oxygen, Z is sulfur, W is oxygen, V is not present, R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen, and X^2 is OH or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

In one aspect, when the compound has the formula VII, U comprises oxygen, Z is sulfur, W is oxygen, V is oxygen, and R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group. In a further aspect, Z is sulfur, U comprises oxygen, W is oxygen, V is oxygen, R^1 is hydrogen or a branched or straight chain C_1 to C_{25} alkyl group, X^1 is hydrogen and X^2 is OH or $OC(O)R^3$, wherein R^3 is a branched or straight chain C_1 to C_{25} alkyl group such as, for example, an oleate group or a palmitate group.

In another embodiment, the compounds having the formula VII are presented in Table 2 below. Where applicable, C_{17} denotes $C_{17}H_{33}$.

TABLE 2

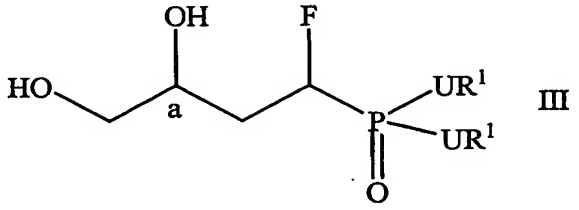
		

Any of the compounds described herein can be the pharmaceutically acceptable salt or ester thereof. Pharmaceutically acceptable salts are prepared by treating the free acid with an appropriate amount of a pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are ammonium hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, ferrous hydroxide, zinc hydroxide, copper hydroxide, aluminum hydroxide, ferric hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, and the like. In one aspect, the reaction is conducted in water, alone or in combination with an inert, water-miscible organic solvent, at a temperature of from about 0 °C to about 100 °C such as at room temperature. The molar ratio of compounds of structural formula I or VII to base used are chosen to provide the ratio desired for any particular salts. For preparing, for example, the ammonium salts of the free acid starting material, the starting material can be treated with approximately one equivalent of pharmaceutically acceptable base to yield a neutral salt.

Ester derivatives are typically prepared as precursors to the acid form of the compounds--as illustrated in the examples below--and accordingly can serve as prodrugs. Generally, these derivatives will be lower alkyl esters such as methyl, ethyl, and the like. Amide derivatives -(CO)NH_2, -(CO)NHR and -(CO)NR_2, where R is an alkyl group defined above, can be prepared by reaction of the carboxylic acid-containing compound with ammonia or a substituted amine.

II. Methods for Preparing LPA Analogs

In one aspect, described herein are methods for preparing compounds having the formula III



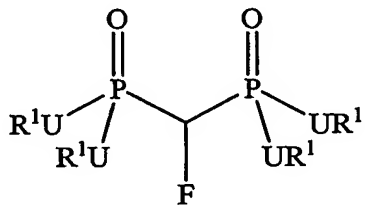
III

wherein each R^1 comprises, independently, hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cationic counterion, or both R^1 form a cyclic or heterocyclic group;

each U comprises, independently, oxygen, sulfur, or NR^1; and

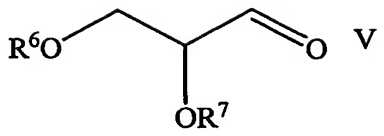
the stereochemistry at carbon a is R or S, or the pharmaceutically acceptable salt or ester thereof. The method involves

(a) reacting a compound having the formula IV



IV

with a compound having the formula V



wherein R^6 and R^7 are protecting groups,

in the presence of a base;

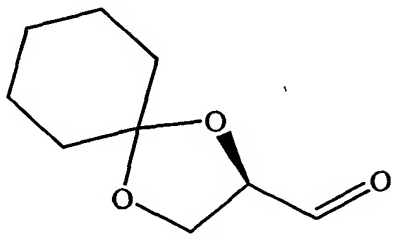
(b) hydrogenating the compound produced in step (a); and

(c) deprotecting the compound produced in step (b) to produce a compound having the formula III.

The compound having the formula III can be prepared by treating $(R_1O)_2(O)PCH_2P(O)(OR_1)_2$ with a base followed by the addition of a fluorinating reagent. Any base that can deprotonate one of the hydrogen atoms present on the methylene group are suitable. Examples of bases include, but are not limited to hydrides such as sodium hydride. The fluorinating agent can be any compound that provides a source of electrophilic fluorine. Examples of fluorinating agents include, but are not limited to, Selectfluor (1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4)) and *N*-fluorodibenzenesulfonimide.

In step (a), compounds IV and V react with one another in the presence of a base. The order at which compound IV, V, and the base are added to one another can vary. In one aspect, the compound having the formula IV is reacted with a base to produce a carbanion species. Any base that can deprotonate the CHF proton in formula IV is suitable. Examples of bases include organolithium compounds such as, for example, n-butyllithium. In this aspect, after the carbanion species is produced, aldehyde compound V is added and condenses with the carbonion species. The condensation product is shown in Figure 1, where two isomers (A and B) are shown. The two isomers can be separated using techniques known in the art such as, for

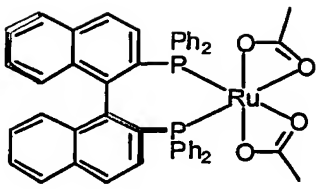
example, by column chromatography. The protecting groups R^6 and R^7 can be any of those disclosed in *Protective Groups in Organic Synthesis* by T.W. Green, John Wiley and Sons, 1981, which is incorporated by reference in its entirety. R^6 and R^7 they can be the same or different. In one aspect, R^6 and R^7 together form a ring. For example, the compound having the formula VI can be used.



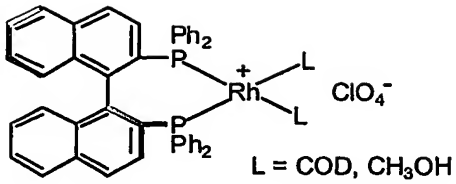
VI

By controlling the stereochemistry of the aldehyde compound V, it is possible to control the stereochemistry at carbon a in formula III. For example, if the aldehyde compound VI is used in step (a), the stereochemistry at carbon a of formula III will be S.

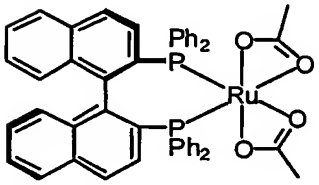
Step (b) involves hydrogenating the alkene group of the condensation product produced after step (a). The reaction generally involves exposing the condensation product to hydrogen in the presence of a catalyst. Numerous hydrogenation catalysts are known in the art. In one aspect, the catalyst is Pd-C. The hydrogenation product is depicted as compound **C** in Figure 1. In another aspect, asymmetric hydrogenation catalysts can be used in step (b). In this aspect, the resultant hydrogenation product can be substantially one enantiomer or diastereomer. The use of asymmetric hydrogenation catalysts are know in the in the art. Examples of asymmetric hydrogenation catalysts useful in the methods described herein include, but are not limited to, the catalysts shown below.



(*S*)-BINAP-Ru(II)



(*S*)-BINAP-Rh(I)



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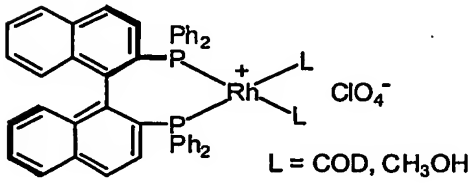
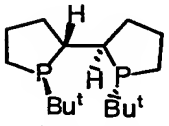
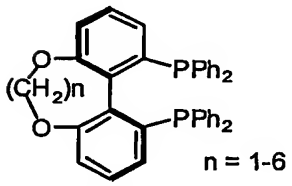


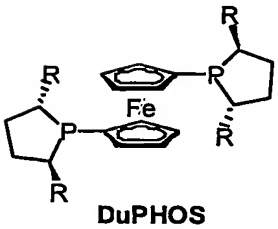
(*R*)-BINAP-Rh(I)



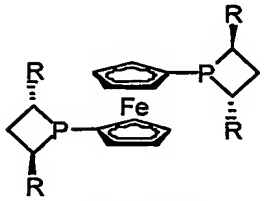
TangPhos



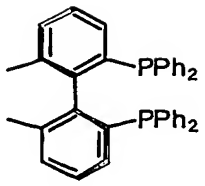
(*S*)-Cn-TunaPhos



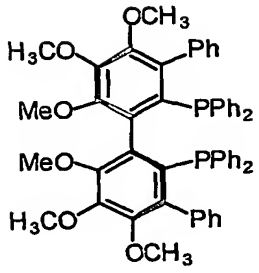
DuPHOS



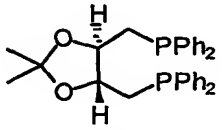
FerroTANE



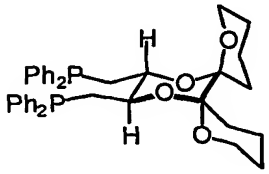
(S)-BIPHEMP



(S)-o-Ph-HexMeO-BIPHEMP



(R,R)-DIOP



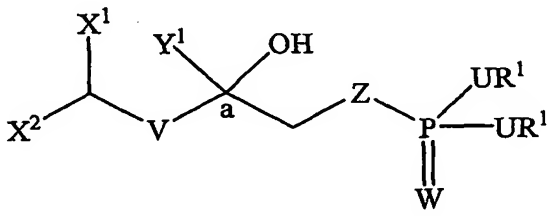
(R,R,R,R)-SK-Phos

After the hydrogenation step (b), the protecting groups R^6 and R^7 are removed. The deprotection can be performed using techniques known in the art. For example, the techniques disclosed in *Protective Groups in Organic Synthesis* by T.W. Green, John Wiley and Sons, 1981, which is incorporated by reference in its entirety, are useful. In one aspect, a catalytic amount of an acid such as, for example, *p*-touenesulfonic acid, can be used. Depending upon the identity of R^6 and R^7, one or both of R^6 and R^7 can be removed (*i.e.*, deprotected). Removal of R^6 and R^7 produces the diol compound III (Figure 1).

The diol compound III can be converted to numerous other compounds using techniques known in the art. In one aspect, reacting the diol compound III with a base followed by a carboxylic acid can convert the primary hydroxyl group to the corresponding ester **D** (Figure 2). In another aspect, the diol compound III can be treated with a base followed by the addition of an organosilane or alkylating agent to convert the primary hydroxyl group to the corresponding silyl or alkoxy compounds **E** and **F**, respectively. Once the primary hydroxyl group is protected, the secondary

hydroxyl group can be converted to another functional group such an alkoxy or ester group. Depicted in Figures 8-10 are various, specific reaction sequences for protecting and deprotecting the hydroxyl groups of compound III. Specific procedures are shown below.

In another aspect, compounds having the formula VII can be prepared by reacting a compound having the formula VIII



VIII

wherein

X^1, X^2, and Y^1 comprises, independently, hydrogen, fluorine, a hydroxyl group, a branched or straight chain C_1 to C_{25} alkyl group, OR^2, $OCH_2CH_2OR^2$, $OC(O)R^3$, or $NC(O)R^3$;

each U comprises, independently, oxygen, sulfur, or NR^1;

V is not present or when V is present, V comprises oxygen or sulfur;

W comprises oxygen or sulfur;

Z comprises oxygen, sulfur, NR^1, CH_2, CHF, CF_2, or $CHOR^2$;

each R^1 comprises, independently, hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cationic counterion, or both R^1 form a cyclic or heterocyclic group;

R^2 comprises hydrogen, a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group or a protecting group;

R^3 comprises a branched or straight chain C_1 to C_{25} alkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group;

or the pharmaceutically acceptable salt or ester thereof,

wherein the stereochemistry at carbon a is either substantially R or substantially S,

with a dehydrating agent.

The dehydrating agent facilitates the cyclization of the compound having the formula VIII to produce cyclic compound VII, which produces water or an alcohol depnding upon the identity of R^1. Using techniques known in the art and described herein, it is possible to control the stereochemistry of the hydroxyl group at carbon a. Examples of dehydrating agents include, but are not limited to, acids such as, for example, Lewis acids (organic acids) or Bronsted acids. In another aspect, the dehydrating agent includes dicyclohexylcarbodiimide (DCC) or *p*-toluenesulfonic acid. Once the cyclic compound VII is produced, the compound can undergo further chemical manipulations known in the art. For example, when W is oxygen in formula VII, the P=O group can be converted to a P=S group by reacting the cyclic compound possessing the P=O group with a compound such as, for example, Lawesson's agent. In one aspect, the reaction schemes depicted in Figures 17-22 can be used to synthesize and derivatize the cyclic compounds described herein.

III. Pharmaceutical Compositions

In one aspect, any of the compounds having the formula I can be combined with at least one pharmaceutically-acceptable carrier to produce a pharmaceutical composition. The pharmaceutical compositions can be prepared using techniques known in the art. In one aspect, the composition is prepared by admixing the compound having the formula I with a pharmaceutically-acceptable carrier. The term "admixing" is defined as mixing the two components together so that there is no chemical reaction or physical interaction. The term "admixing" also includes the chemical reaction or physical interaction between the compound having the formula I and the pharmaceutically-acceptable carrier.

Pharmaceutically-acceptable carriers are known to those skilled in the art. These most typically would be standard carriers for administration to humans, including solutions such as sterile water, saline, and buffered solutions at physiological pH.

Molecules intended for pharmaceutical delivery may be formulated in a pharmaceutical composition. Pharmaceutical compositions may include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the molecule of choice. Pharmaceutical compositions may also include one or more active ingredients such as antimicrobial agents, antiinflammatory agents, anesthetics, and the like.

The pharmaceutical composition may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated. Administration may be topically (including ophthalmically, vaginally, rectally, intranasally).

Preparations for administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles, if needed for collateral use of the disclosed compositions and methods, include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles, if needed for collateral use of the disclosed compositions and methods, include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like.

Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

It will be appreciated that the actual preferred amounts of active compound in a specified case will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, and the particular situs and mammal being treated. Dosages for a given host can be determined using

conventional considerations, e.g. by customary comparison of the differential activities of the subject compounds and of a known agent, e.g., by means of an appropriate conventional pharmacological protocol. Physicians and formulators, skilled in the art of determining doses of pharmaceutical compounds, will have no problems determining dose according to standard recommendations (Physicians Desk Reference, Barnhart Publishing (1999).

IV. Methods of Use

LPA is an important lysophospholipid mediator produced by activated platelets. LPA elicits a variety of biological effects, which includes platelet aggregation, smooth muscle contraction, changes in cell morphology, and stimulation of cell growth and proliferation. Moreover, the observation that LPA is the key cell proliferation factor overproduced in ascites of human ovarian cancer patients has led to the validation of the G-protein-coupled seven-transmembrane domain LPA receptors as targets for cancer therapy. In addition, phosphatidic acid (PA), the product of the action of phospholipase D on phosphatidylcholine and other phospholipids, is well-established as an important intermediate in the biosynthesis of phosphoglycerides as a regulator of phosphoinositide metabolism, in physiological processes from cell growth to protein trafficking.

The compounds described herein possess improved properties over LPA. For example, the compounds described herein have prolonged biological activity by altering pharmocokinetics, metabolism, and ligand binding.

In one aspect, the compounds described herein can be used as long-lasting agonists, antagonists, or enzyme inhibitors.

In one aspect, the compounds described herein are a PPARγ agonist. For example, the compounds described herein can stimulate PPAR-responsive element reporter expression, the endogenous PPARγ-controlled gene CD36, and induce monocyte lipid accumulation from oxidized LDL via the CD36 scavenger receptor. The techniques disclosed in McIntyre *et al. Proc. Nat. Acad. Sci.* 100, pp 131-136,

Jan. 2003, which is incorporated by reference in its entirety, can be used to determine if the compounds described herein can be used as PPARγ agonists.

In another aspect, the compounds described herein can inhibit lipid phosphatase activity, lipid kinase, or phopholipase in order to treat or prevent a disease in a subject.

In one aspect, described herein are methods for improving wound healing in a subject in need of such improvement by contacting the wound of a mammal with any of the compounds described herein. The compounds or pharmaceutical compositions described herein can be delivered onto cells, tissues, and/or organs, for example, by injection, spraying, squirting, brushing, painting, coating, and the like. Delivery can also be via a cannula, catheter, syringe with or without a needle, pressure applicator, pump, and the like. In one aspect, any of the compounds described herein can be incorporated into a sponge, dressing, bandage, hydrogel, or cream in order to enhance wound healing.

In another aspect, described herein are methods for treating or preventing in a subject a disease by administering to the subject any of the compounds described herein. Examples of diseases treated by the compounds described herein include, but are not limited to, cancer and diabetes. In one aspect, the compounds described herein can be used to treat ovarian cancer.

In a further aspect, described herein are methods for reducing inflammation or an allergic response in a subject by administering to the subject the compound any of the compounds described herein. In another aspect, described herein are methods for increasing or altering cardiovascular function in a subject by administering to the subject any of the compounds described herein. For example, the compounds can vasodilate or vasoconstrict blood vessels depending upon the selection of the compound.

In another aspect, described herein are methods for eliciting or inhibiting platelet aggregation in a subject by administering to the subject any of the compounds described herein.

In an additional aspect, described herein are methods for maintaining or terminating embryonic development in a subject by administering to the subject any of the compounds described herein.

Described herein are methods for determining the activity of lysophosphatidic acid or phosphatidic acid. The method involves (a) measuring the activity of any of the compounds described herein; and (b) measuring the same activity of lysophosphatidic acid or phosphatidic acid.

In one aspect, when a compound having the formula I has an acyl group, a reporter group is present on the acyl group. In one aspect, the reporter group is attached to the acyl group via a tether. Examples of reporter groups include, but are not limited to, a fluorescent tag, a radiolabel, a targeting moiety, a lipid, a peptide, a radionuclide chelator with a radionuclide, a spin-label, a glass surface, a plastic surface, or a combination thereof. Examples of fluorescent groups include, but are not limited to, BODIPY, fluorescein, or NBD-hexanoyl. Examples of radiolabels include, but are not limited to, 125I-tyrosine, 3H-acetyl, or ^{14}C-acetyl. Examples of targeting moieties include, but are not limited to, 6-aminohexanoyl (Z) derivatives of integrin targeting peptide, such as ZYRGDS, Z-tat decapeptide for cell penetration, Z-GFLG for lysosome targeting, or HA oligosaccharide for CD-44 cancer targeting. Examples of spin labels include, but are not limited to, proxyl or doxyl groups. Examples of glass surfaces include, but are not limited to, glass silanized with an epoxy, activated ester, or thiol-reactive electrophilic functional groups, beads, or coverslips. Examples of plastics include, but are not limited to, plasma-etched polypropylene, chemically-modified polystyrene, or any other plastic material. In this aspect, the LPA analog having a reporter group can be used to target discovery of diseases, which can ultimately lead to drug discovery.

In another aspect, the compounds described herein can be used to maintain, increase, or inhibit cell growth or proliferation in cultures. In this aspect, the compounds can be used in tissue engineering.

In another aspect, the compounds described herein can be used to identify edg

and non-edg receptor cites.

The following is a partial list of the many activities that can be determined in the present screening method:

1. Receptor agonist/antagonist activity:

A compendia of examples of specific screens for measuring these activities can be found in: "The RBI Handbook of Receptor Classification and Signal Transduction" K.J. Watling, J.W. Kebebian, J.L. Neumeyer, eds. Research Biochemicals International, Natick, MA, 1995, and references therein. Methods of analysis can be found in: T. Kenakin "Pharmacologic Analysis of Drug-Receptor Interactions" 2nd Ed. Raven Press, New York, 1993, and references therein. In one aspect, agonists or antagonists of lysophosphatidic acid binding to or activating lysophosphatidic acid receptors of the edg class in a cell.

2. Enzyme inhibition:

A compendia of examples of specific screens for measuring these activities can be found in: H. Zollner "Handbook of Enzyme Inhibitors", 2nd Ed. VCH Weinheim, FRG, 1989, and references therein.

3. Central nervous system, autonomic nervous system (cardiovascular and gastrointestinal tract), antihistaminic, anti-inflammatory, anaesthetic, cytotoxic, and antifertility activities:

A compendia of examples of specific screens for measuring these activities can be found in: E.B. Thompson, "Drug Bioscreening: Drug Evaluation Techniques in Pharmacology", VCH Publishers, New York, 1990, and references therein.

4. Anticancer activities:

A compendia of examples of specific screens for measuring these activities can be found in: I.J. Fidler and R.J. White "Design of Models for Testing Cancer Therapeutic Agents", Van Nostrand Reinhold Company, New York, 1982, and references therein.

5. Antibiotic and antiviral (especially anti-HIV) activities:

A compendia of examples of specific screens for measuring these activities can be found in: "Antibiotics in Laboratory Medicine", 3rd Ed., V. Lorian, ed. Williams and Wilkens, Baltimore, 1991, and references therein. A compendia of anti-HIV screens for measuring these activities can be found in: "HIV Volume 2: Biochemistry, Molecular Biology and Drug Discovery", J. Karn, ed., IRL Press, Oxford, 1995, and references therein.

6. Immunomodulatory activity:

A compendia of examples of specific screens for measuring these activities can be found in: V. St. Georgiev (1990) "Immunomodulatory Activity of Small Peptides" Trends Pharm. Sci. 11, 373-378.

7. Pharmacokinetic properties:

The pharmacological activities assayed in the screening method include half-life, solubility, or stability, among others. For example, methods of analysis and measurement of pharmacokinetic properties can be found in: J.-P. Labaune "Handbook of Pharmacokinetics: Toxicity Assessment of Chemicals", Ellis Horwood Ltd., Chichester, 1989, and references therein.

The compounds described herein are stable when compared to LPA. For example, acyl migration occurs in LPA, which complicates studies of positional specificity. By testing any of the compounds described herein, it is possible to identify potential activities of LPA. Once the potential activity has been identified, it is possible to test the activity with LPA. Thus, the compounds described herein are useful tools in determining other potential activities of LPA, which will ultimately lead to the treatment or prevention of additional diseases.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, and methods described and claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the scope of what

the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric. There are numerous variations and combinations of reaction conditions, e.g., component concentrations, desired solvents, solvent mixtures, temperatures, pressures and other reaction ranges and conditions that can be used to optimize the product purity and yield obtained from the described process. Only reasonable and routine experimentation will be required to optimize such process conditions.

I. Synthesis of α-Difluoro-Analogs of LPA

One approach to the synthesis of difluoromethylene anlogs of LPA is depicted in Figure 3. The addition reaction of diethyl iododifluoromethylenephosphonate **3** to allyl alcohol catalyzed by tetrakis(triphenylphosphine)-palladium in hexane gave the corresponding iodohydrin **4** in 79% yield. However, treatment of the iodohydrin **4** with diluted K_2CO_3/MeOH solution for 5 min at room temperature provided the desired epoxide **5** in good yield (72%). Next, terminal epoxide **5** was employed for the HKR reaction, constituting the first application of HKR in a substrate containing both fluorine and phosphonate functionalities. Few examples of HKR with fluorine-containing epoxides were found, and no HKR substrates have been reported for phosphonate or phosphate-containing epoxides. The reaction of racemic epoxide with 0.45 equiv of H_2O in a minimum volume of THF in the presence of 1.0 mol% of (*R,R*)-**6**-OAc gave diol **7a** in 99% ee and 69% isolated yield. Similarly, catalyst (*S,S*)-**6**-OAc provided the opposite configuration of diol **7b** in 99% ee and 70% yield. The epoxide and diol were readily separated by flash chromatography, providing an excellent example of the scope and utility of the HKR process.

Regioselective acylation at the primary hydroxyl of the 1,2-diol was readily accomplished. Thus, treatment of **7a** with 0.95 equiv of oleic acid and 1.2 equiv DCC and DMAP in CH_2Cl_2 at 0 °C gave **9a** in 42% yield after chromatography, accompanied by a small amount of diester (Figure 4). When the reaction was

performed at rt, the ratio of primary ester to diester decreased. Diesters bearing identical acyl chains, e.g., **11a** and **11b**, could be obtained in 73% yield, with 2.4 equiv of oleic acid in the presence of excess DCC and DMAP in CH_2Cl_2.

Dealkylation of phosphonic acid diethyl esters was achieved by treatment with excess bromotrimethylsilane (10.0 equiv) for 8 hr at rt; interestingly, use of only 3.0 equiv of TMSBr did not result in complete dealklylation. After hydrolysis by aqueous methanol (95%) followed by ion exchange chromatography, the sodium salts of LPA analogues **10** and PA analogues **12** were obtained in essentially quantitative yield.

The enantiomeric purity of diols **7a** and **7b** was determined by Mosher's ester method, and optical purities were measured by integration of the ^1H NMR. The double doublet at δ 4.35 ppm in **12a** was shifted to δ 4.44 ppm in **12b**. There was no detectable signal at δ 4.44 ppm in **12a**, nor at δ 4.35 ppm in **12b**, indicating that each diol had been obtained in >99% ee.

General Procedure. Chemicals were obtained from Aldrich and Acros and were used without prior purification. Solvents used were of reagent grade and were distilled before use: THF was distillated from sodium wire, and methylene chloride was distillated from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. ^1H and ^{13}C spectra were recorded at 25°C at 400 MHz (^1H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F). Chemical shifts are given in ppm with TMS as

internal standard (δ=0.00); ^{31}P, 85% H_3PO_4 (δ=0.00); ^{19}F, $CFCl_3$ (δ=0.00). Optical Rotations were measured on Perkin Elmer 343 Polarimeter.

Diethyl [1,1-difluoro-3-iodo-4-hydroxy-butyl]phosphonate 4. To a stirred solution of $Pd(PPh_3)_4$ (0.718 g, 0.621 mmol, 0.026 eq.) and allyl alcohol (2.774 g, 47.76 mmol) in hexane (20 mL) at rt was added diethyl iododifluoromethylphosphonate (7.499 g, 23.88 mmol), and the resultant mixture was stirred for 10 min. The reaction mixture was dissolved in 100 mL of hexane/ethyl acetate (1:1). The resulting solid was removed by filtrate and the solid was washed with hexane/ethyl acetate solvent. The combined solution were then concentrated to give a residue which was purified

by flash chromatograph on silica gel (HE:AE = 1:1, R_f = 0.26) gave a colorless liquid (7.010 g, 18.844 mmol, 79%). ^{1}H NMR($CDCl_3$): 4.48 (m, 1H), 4.27 (m, 4H), 3.75 (d, J = 5.2 Hz, 2H), 2.98 (m, 1H), 2.71 (m, 1H), 2.01 (br, 1H), 1.36 (m, 6H). ^{13}C NMR($CDCl_3$): 119.79 (td, J = 262.36, 215.50 Hz), 67.94 (s), 64.86 (dd, J = 9.96, 3.12 Hz), 40.36 (td, J = 19.91, 16.09 Hz), 23.54 (s), 16.27 (d, J = 5.33 Hz). ^{19}F NMR($CDCl_3$): -110.77 (1F, dddd, J = 297.29, 105.37, 39.51, 13.17 Hz), -112.03 (1F, dddd, J = 297.29, 105.37, 39.51, 13.17 Hz). ^{31}P NMR($CDCl_3$): 6.94 (t, J = 105.41 Hz).

Diethyl [1,1-difluoro-3,4-epoxy-butyl]phosphonate 5. K_2CO_3 (0.245 g, 1.774 mmol) was added to a solution of compound 4 (0.110 g, 0.296 mmol) in MeOH (15 mL). The reaction mixture was stirred for 10 min at rt and then diluted with water (15 mL) and extracted with CH_2Cl_2 (20 mL×3). The organic phase was dried (Na_2SO_4), filtrated, and concentrated in vacuo. The residue was purified by flash column chromatograph to give epoxide as a colorless oil (52 mg, 0.213 mmol, 72%, HE:AE = 1:1, R_f = 0.27). ^{1}H NMR($CDCl_3$): 4.25 (m, 4H), 3.20 (m, 1H), 2.80 (t, J = 4.5 Hz, 1H), 2.53 (dd, J = 2.4, 7.6 Hz, 1H), 2.37 (m, 1H), 2.17 (m, 1H), 1.35 (t, J = 7.2 Hz, 6H). ^{13}C NMR($CDCl_3$): 119.79 (td, J = 262.36, 215.50 Hz), 64.62 (d, J = 6.84 Hz), 46.24 (s), 45.54 (dd, J = 13.88, 6.94 Hz), 37.92 (m), 16.32 (d, J = 5.03 Hz). ^{19}F NMR($CDCl_3$): -110.40 (1F, dddd, J = 302.56, 105.37, 21.07, 17.31 Hz), -111.48 (1F, dddd, J = 302.56, 105.37, 21.07, 17.31 Hz). ^{31}P NMR($CDCl_3$): 7.24 (t, J = 105.41 Hz). MS (CI) m/z 245.0 (M^++1, 100.00). HRMS, M^++1, Found: 245.0751. Calcd for $C_8H_{16}F_2O_5P$, 245.0754.

Hydrolytic Kinetic Resolution of Epoxide 5 with (R,R) catalyst. A 10 mL flask equipped with a stir bar was charged with (*R,R*)-1 (20.2 mg, 33 μmol, 0.01 equiv). The catalyst was dissolved in 0.4 mL of PhMe and treated with AcOH (8 μL, 0.132 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in epoxide (0.816 g, 3.344 mmol) and THF (120 μL) at room temperature,

the reaction flask was cooled to 0°C, and H_2O (27.1 μL, 1.505 mmol, 0.45 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir 14 h. Chromatograph on silicon gel get (*R*)-epoxide (0.400 g, 1.637 mmol, 98%, R_f = 0.27, HE:AE = 1:1) and (S)-diol (0.302 g, 1.154 mmol, 69%, R_f = 0.27, AE). The ee value of the diol was determined to be > 99.0% by Mosher ester.

Diethyl [1,1-Difluoro-3 (S), 4-dihydroxybutyl]phosphonate 7a. Colorless liquid. ^{1}H NMR($CDCl_3$): 4.24 (m, 4H), 4.10 (m, 1H), 3.62 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.49 (dd, *J* = 10.8, 6.0 Hz, 1H), 2.21 (m, 2H), 1.35 (m, 6H). ^{13}C NMR($CDCl_3$): 120.17 (td, *J* = 260.45, 215.20 Hz), 66.26 (s), 65.97 (m), 65.04 (dd, *J* = 24.54, 6.94 Hz), 39.10 (m), 16.29 (d, *J* = 5.43 Hz). ^{19}F NMR($CDCl_3$): -106.69 (1F, ddt, *J* = 302.56, 103.86, 16.93 Hz), -111.10 (1F, ddt, *J* = 302.56, 103.86, 16.93 Hz). ^{31}P NMR($CDCl_3$): 8.39 (t, *J* = 107.51 Hz). MS (CI) m/z 263.1 (M^++1,100.00), 217.0 (M^+-C_3H_8, 3.59). HRMS, M^++1, Found: 263.0876. Calcd for $C_8H_{18}F_2O_5P$, 263.0860. $[\alpha]^{20}_D$ = -10.39 (c=0.38, MeOH).

Diethyl [1,1-difluoro-3(R)-3,4-epoxy-butyl]phosphonate 8a. Colorless liquid. ^{1}H NMR($CDCl_3$): 4.22 (m, 4H), 3.15 (m, 1H), 2.77 (dd, *J* = 4.8, 4.0 Hz, 1H), 2.49 (dd, *J* = 4.4, 2.0 Hz, 1H), 2.33 (m, 1H), 2.14 (m, 1H), 1.32 (m, 6H). ^{13}C NMR($CDCl_3$): 119.52 (td, *J* = 260.75, 216.20 Hz), 64.56 (d, *J* = 6.84 Hz), 46.15 (s), 45.45 (m), 37.86 (m), 16.24 (d, *J* = 6.13 Hz). ^{19}F NMR($CDCl_3$): -110.48 (1F, dddd, *J* = 302.56, 105.37, 21.07, 15.81 Hz), -111.41 (1F, dddd, *J* = 302.56, 105.37, 21.07, 15.81 Hz). ^{31}P NMR($CDCl_3$): 7.21 (t, *J* = 105.41 Hz). $[\alpha]^{20}_D$ = +6.53 (c=1.50, MeOH).

Hydrolytic Kinetic Resolution of Epoxide 5 with (S,S) catalyst. A 10 mL flask equipped with a stir bar was charged with (*S,S*)-1 (27.7 mg, 46 μmol, 0.01 equiv). The catalyst was dissolved in 0.5 mL of PhMe and treated with AcOH (10 μL, 0.183 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in epoxide (1.119 g, 4.586 mmol) and THF (150 μL) at room temperature, the reaction flask was cooled to 0°C, and H_2O (37.2 μL, 2.064 mmol, 0.45 equiv) was

added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir 14 h. Chromatograph on silicon gel get (*S*)-epoxide (0.549 g, 2.250 mmol, 98%) and (S)-diol (0.422 g, 1.611 mmol, 70%). The ee of the diol was determined to be > 99.0% by Mosher ester.

Diethyl [1,1-Difluoro-3 (R), 4-dihydroxybutyl]phosphonate 7b. Colorless liquid. ^{1}H NMR($CDCl_3$): 4.29-4.22 (m, 4H), 4.08 (m, 1H), 3.77 (br, 2H), 3.60 (dd, J = 11.2, 3.6 Hz, 1H), 3.47 (dd, J = 11.2, 6.4 Hz, 1H), 2.29-2.12 (m, 2H), 1.33 (m, 6H). ^{13}C NMR($CDCl_3$): 120.14 (td, J = 260.05, 214.80 Hz), 66.22 (s), 65.97 (m), 65.00 (dd, J = 22.22, 6.94 Hz), 38.89 (td, J = 19.91, 15.29 Hz), 16.25 (d, J = 5.33 Hz). ^{19}F NMR($CDCl_3$): -107.01 (1F, ddt, J = 302.56, 105.37, 17.31 Hz), -111.09 (1F, ddt, J = 302.56, 105.37, 17.31 Hz). ^{31}P NMR($CDCl_3$): 8.29 (dd, J = 110.75, 105.41 Hz). $[\alpha]^{20}_D$ = +9.98 (c=0.48, MeOH).

Diethyl [1,1-difluoro-3(S)-3,4-epoxy-butyl]phosphonate 8b. Colorless liquid. ^{1}H NMR($CDCl_3$): 4.22 (m, 4H), 3.15 (m, 1H), 2.77 (dd, J = 4.8, 4.0 Hz, 1H), 2.49 (dd, J = 4.4, 2.0 Hz, 1H), 2.33 (m, 1H), 2.14 (m, 1H), 1.32 (m, 6H). ^{13}C NMR($CDCl_3$): 119.52 (td, J = 260.75, 216.20 Hz), 64.56 (d, J = 6.84 Hz), 46.15 (s), 45.45 (m), 37.86 (m), 16.24 (d, J = 6.13 Hz). ^{19}F NMR($CDCl_3$): -110.48 (1F, dddd, J = 302.56, 105.37, 21.07, 15.81 Hz), -111.41 (1F, dddd, J = 302.56, 105.37, 21.07, 15.81 Hz). ^{31}P NMR($CDCl_3$): 7.21 (t, J = 105.41 Hz). $[\alpha]^{20}_D$ = -6.11 (c=0.72, MeOH).

Diethyl [1,1-Difluoro-3 (S)-hydroxyl-4-(oleoyl)butyl]phosphonate 9a. To a solution of diol (67 mg, 0.256 mmol) and oleic acid (68 mg, 0.243 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of DCC (63 mg, 0.307 mmol) and DMAP (9 mg, 0.154 mmol) in dry CH_2Cl_2 (1 mL) at 0°C. The solution was stirred for 16 h at 0°C, filtered, concentrated *in vacuo*, and the residue was purified on silica gel (n-hexane/ethyl acetate, HE:AE = 2:1, R_f = 0.17) to afford ester (56 mg, 0.108 mmol, 42%) as a waxy solid. ^{1}H NMR($CDCl_3$): 5.32 (m, 2H), 4.32-4.24 (m, 5H), 4.09 (d, J = 5.2 Hz, 2H), 3.82 (br, 1H), 2.32 (m, 2H), 2.22 (m, 2H), 1.97 (m, 4H), 1.58 (t, J = 7.2 Hz, 2H), 1.38 (m, 6H), 1.27 (m, 20H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.66 (s), 129.98 (s), 129.72 (s), 67.23 (s), 65.08 (dd, J = 33.79, 6.94 Hz), 63.98 (m),

39.76 (td, J = 19.21, 16.09 Hz), 34.07 (s), 31.88 (s), 29.74 (s), 29.67 (s), 29.50 (s), 29.20 (s), 29.14 (s), 29.08 (s), 27.19 (s), 27.14 (s), 24.87 (s), 22.66 (s), 16.35 (d, J = 5.43 Hz), 14.08 (s). ^{19}F NMR($CDCl_3$): -106.19 (1F, ddt, J =304.07, 102.74, 15.81 Hz), -111.43 (1F, ddt, J = 304.07, 102.74, 15.81 Hz). ^{31}P NMR($CDCl_3$): 8.42 (dd, J = 109.78, 101.04 Hz). $[\alpha]^{20}_D$ = -1.67 (c=0.12, MeOH).

Diethyl [1,1-Difluoro-3 (R)-hydroxyl-4-(oleoyl)butyl]phosphonate 9b. Colorless liquid. ^{1}H NMR($CDCl_3$): 5.32 (m, 2H), 4.32-4.23 (m, 5H), 4.08 (d, J = 4.8 Hz, 2H), 3.83 (br, 1H), 2.32 (m, 2H), 2.23 (m, 2H), 1.97 (m, 4H), 1.60 (t, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 6H), 1.25 (m, 20H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.65 (s), 129.96 (s), 129.70 (s), 120.17 (td, J = 260.45, 215.20 Hz), 67.22 (s), 65.06 (dd, J = 32.98, 7.64 Hz), 63.96 (m), 39.71 (td, J = 19.91, 16.09 Hz), 34.07 (s), 31.86 (s), 29.73 (s), 29.66 (s), 29.48 (s), 29.28 (s), 29.13 (s), 29.06 (s), 27.18 (s), 27.13 (s), 24.85 (s), 22.64 (s), 16.33 (d, J = 5.43 Hz), 14.06 (s). ^{19}F NMR($CDCl_3$): -106.28 (1F, ddt, J = 302.94, 101.98, 16.18 Hz), -111.43 (1F, ddt, J = 302.94, 101.98, 16.18 Hz). ^{31}P NMR($CDCl_3$): 8.40 (dd, J = 109.78, 102.17 Hz). MS (CI) m/z 527.1 (M^++1,12.66), 481.1 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 527.3319. Calcd for $C_{26}H_{50}F_2O_6P$, 527.3316. $[\alpha]^{20}_D$ = +1.36 (c=0.22, MeOH).

Sodium [1,1-Difluoro-3 (S)-hydroxyl-4-(oleoyl)butyl]phosphonate 10a. Thoroughly dried diethyl precursor **9a** (30 mg, 0.057 mmol, 5 h under high vacuum) was dissolved in anhydrous methylene chloride (0.2 mL) at room temperature. Bromotrimethylsilane (38 μL, 0.290 mmol) was added with a dry syringe and stirred 4 h. TLC indicated that all of the reactant had disappeared, then the solvent removed under reduced pressure and dried under vacuum. The residue was dissolved in 95% methanol (1 mL) for 1h and concentrated in vacuuo got colorless oil, which made a cloudy solution when dissolved in water. The water turned to clear after added 1-2 drops triethylamine (PH = 7-8). This solution was absorbed to a sodium ion-exchange column (DOWEX 50WX8-200 resin, neutral Na^+ form), and eluted with water. The fraction was lyophilized to give a colorless liquid (28 mg, 0.055 mmol, 96%). ^{1}H NMR(CD_3OD): 5.28 (m, 1H), 5.16 (m, 2H), 3.49 (dd, J = 11.2, 4.8 Hz, 1H), 3.40 (dd,

J = 11.2, 5.2 Hz, 1H), 2.33 (m, 2H), 2.16 (td, J = 7.2, 1.6 Hz, 2H), 1.84 (m, 4H), 1.44 (m, 2H), 1.15-1.11 (m, 20H), 0.72 (t, J = 6.6 Hz, 3H). ^{13}C NMR(CD_3OD): 174.04 (s), 130.88 (s), 130.79 (s), 67.71 (s), 39.72 (td, J = 19.91, 16.09 Hz), 35.22 (s), 35.08 (s), 33.06 (s), 30.84 (s), 30.78 (s), 30.61 (s), 30.45 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.12 (s), 28.13 (s), 25.90 (s), 23.74 (s), 14.47 (s). ^{19}F NMR(CD_3OD): -113.96 (m). ^{31}P NMR($CDCl_3$): 5.74 (dd, J = 102.01 Hz). $[\alpha]^{20}_D$ = +4.83 (c=0.60, MeOH).

Sodium [1,1-Difluoro-3 (R)-hydroxyl-4-(oleoyl)butyl]phosphonate 10b. Following the above procedure with precursor 9b gave a colorless oil with analogous spectral properties but with $[\alpha]^{20}_D$ = -5.27 (c=0.22, MeOH).

Diethyl [1,1-Difluoro-3 (S), 4-Bis(oleoyl)butyl]phosphonate 11a. To a solution of diol (35 mg, 0.134 mmol) and oleic acid (91 mg, 0.322 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of DCC (0.347 mmol) and DMAP (0.347 mmol) in dry CH_2Cl_2 (1 mL) at rt. The solution was stirred for 16 h at rt, filtered, concentrated *in vacuo*, and the residue was purified on silica gel (n-hexane/ethyl acetate =3:1, R_f = 0.33) to ester (77 mg, 0.098 mmol, 73%) as a colorless oil. ^{1}H NMR($CDCl_3$): 5.48 (m, 1H), 5.31 (m, 4H), 4.30-4.20 (m, 5H), 4.04 (dd, J = 11.6, 5.6 Hz, 1H), 2.38 (m, 2H), 2.27 (m, 4H), 1.98 (m, 8H), 1.56 (m, 4H), 1.34 (t, J = 8.0 Hz, 6H), 1.21 (m, 40H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.17 (s), 172.47 (s), 129.94 (s), 129.66 (s), 64.98 (m), 64.72 (dd, J = 6.94, 6.13 Hz), 64.53 (s), 34.93 (td, J = 19.91, 15.38 Hz), 34.18 (s), 33.97 (s), 31.85 (s), 29.71 (s), 29.67 (s), 29.47 (s), 29.27(s), 29.14 (s), 29.07 (s), 29.00 (s), 27.16 (s), 27.13 (s), 24.79 (s), 24.71 (s), 22.63(s), 16.32 (d, J = 5.33 Hz), 14.05 (s). ^{19}F NMR($CDCl_3$): -111.63 (1F, dddd, J =260.41, 65.86, 23.71, 14.18 Hz), -112.40 (1F, ddt, J = 260.41, 65.86, 23.71, 14.18 Hz). ^{31}P NMR($CDCl_3$): 7.18 (t, J = 105.41 Hz). $[\alpha]^{20}_D$ = -1.02 (c=0.88, MeOH).

Diethyl [1,1-Difluoro-3 (R), 4-Bis(oleoyl)butyl]phosphonate 11b. ^{1}H NMR($CDCl_3$): 5.48 (m, 1H), 5.31 (m, 4H), 4.31-4.21 (m, 5H), 4.04 (dd, J = 11.6, 5.6 Hz, 1H), 2.38 (m, 2H), 2.28 (m, 4H), 1.98 (m, 8H), 1.58 (m, 4H), 1.35 (t, J = 8.0 Hz, 6H), 1.21 (m, 40H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.17 (s), 172.48 (s), 129.95 (s), 129.67 (s), 65.00 (m), 64.71 (dd, J = 6.94, 6.13 Hz), 64.54 (s), 34.48

(td, J = 19.21, 16.09 Hz), 34.19 (s), 31.85 (s), 29.72 (s), 29.67 (s), 29.47 (s), 29.27 (s), 29.15 (s), 29.08 (s), 29.05 (s), 29.01 (s), 27.17 (s), 27.13 (s), 24.80 (s), 24.72 (s), 22.63 (s), 16.32 (d, J = 5.43 Hz), 14.05 (s). ^{19}F NMR($CDCl_3$): -111.63 (1F, dddd, J =260.41, 65.86, 23.71, 14.18 Hz), -112.40 (1F, ddt, J = 260.41, 65.86, 23.71, 14.18 Hz). ^{31}P NMR($CDCl_3$): 7.18 (t, J = 105.41 Hz). MS (CI) m/z 791.4 (M^++1,100.00), 509.2 (M^+-$C_{17}H_{33}CO_2$, 18.15). HRMS, M^+, Found: 790.5684. Calcd for $C_{44}H_{81}F_2O_7P$, 790.5688. $[\alpha]^{20}_D$= +1.47 (c=0.51, MeOH).

Sodium [1,1-difluoro-3 (R), 4-Bis(oleoyl)butyl]phosphonate 12b. Thoroughly dried precursor (35 mg, 0.035 mmol, 5 h under high vacuum) was dissolved in anhydrous methylene chloride (0.2 mL) at room temperature. Bromotrimethylsilane (46 μL, 0.35 mmol) was added with a dry syringe and stirred 4 h. TLC indicated that all of the reactant had disappeared, then the solvent removed under reduced pressure and dried under vacuum. The residue was dissolved in 95% methanol (1 mL) for 1h and concentrated in vacuuo got colorless oil, which made a cloudy solution when dissolved in water. The water turned to clear after added 1-2 drops triethylamine (PH = 7-8). This solution was absorbed to a sodium ion-exchange column (DOWEX 50WX8-200 resin, neutral Na^+ form), and eluted with water. The fraction was lyophilized to give product (32 mg, 0.041 mmol, 93%). ^{1}H NMR(CD_3OD): 5.36 (m, 1H), 5.18 (m, 4H), 4.24 (d, J = 11.2 Hz, 1H), 3.89 (m, 1H), 2.26 (m, 2H), 2.14 (m, 4H), 1.86 (m, 8H), 1.44 (m, 4H), 1.16-1.13 (m, 40H), 0.73 (m, 3H). ^{13}C NMR(CD_3OD): 174.65 (s), 174.11 (s), 130.91 (s), 130.77 (s), 66.80 (m), 65.88 (s), 65.32 (m), 35.16 (s), 34.89 (s), 33.10 (s), 30.89 (s), 30.86 (s), 30.67 (s), 30.50 (s), 30.41 (s), 30.36 (s), 30.26 (s), 30.22 (s), 30.18 (s), 28.20 (s), 26.00 (s), 25.93 (s), 23.77 (s). ^{19}F NMR(CD_3OD): -114.20 (m). ^{31}P NMR(CD_3OD): 5.88 (t, J = 252.80 Hz). $[\alpha]^{20}_D$= +0.87 (c=0.58, MeOH).

Sodium [1,1-Difluoro-3 (S), 4-Bis(oleoyl)butyl]phosphonate 12a was obtained similarly, $[\alpha]^{20}_D$= -0.52 (c=0.29, MeOH).

Diethyl [1,1-Difluoro-3 (S)-[(S)- α-methoxy-α-(trifluoromethyl)phenylacetyl]4-(oleoyl)butyl]phosphonate 13a. A solution of alcohol **9a** (8 mg, 0.015 mmol) and

(R)- α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (15 mg, 0.061 mmol) in pyridine (1 mL) was stirred for 20 at rt. The mixture was diluted with CH_2Cl_2 (10 mL), washed with aq. $NaHCO_3$ (3 mL), dried, filtered, and concentrated *in vacuo*. Flashed chromatography on silicon gel gave the corresponding MTPA ester as colorless oil (10 mg, 0.0135 mmol, 89%, HE:AE/2:1, $R_f = 0.27$). ^1H NMR($CDCl_3$): 7.52-7.49 (m, 2H), 7.39-7.35 (m, 3H), 5.76-5.71 (m, 1H), 5.34-5.31 (m, 2H), 4.35 (dd, J = 12.0, 3.6 Hz, 1H), 4.29-4.23 (m, 4H), 4.03 (dd, J = 12.0, 5.6 Hz, 1H), 3.53 (s, 3H), 2.56-2.41 (m, 2H), 2.18 (t, J = 7.6 Hz, 2H), 1.98 (m, 4H), 1.52 (m, 2H), 1.38 (t, J = 6.8 Hz, 6H), 1.25 (m, 20H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.01 (s), 165.66 (s), 131.98 (s), 130.02 (s), 129.72 (s), 129.61 (s), 128.36 (s), 127.34 (s), 67.58 (m), 64.91 (d, J = 6.13 Hz), 64.14 (s), 55.49 (s), 34.98 (td, J = 20.71, 15.38 Hz), 33.78 (s), 31.89 (s), 29.76 (s), 29.70 (s), 29.52 (s), 29.31 (s), 29.15 (s), 29.06 (s), 27.22 (s), 27.17 (s), 24.63 (s), 22.67 (s), 16.35 (d, J = 5.33 Hz), 14.09 (s). ^{19}F NMR($CDCl_3$): -72.07 (s), -111.84 (1F, dtd, J =105.37, 22.58, 15.43 Hz), -112.11 (1F, ddt, J = 105.37, 22.58, 15.43 Hz). ^{31}P NMR($CDCl_3$): 6.92 (t, J = 104.28 Hz).

Diethyl [1,1-Difluoro-3 (R)-[(S)- α-methoxy-α-(trifluoromethyl)phenylacetyl]4-(oleoyl)butyl]phosphonate 13b. A solution of alcohol **9b** (18 mg, 0.034 mmol) and (R)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (35 mg, 0.137 mmol) in pyridine (2 mL) was stirred for 20 at rt. The mixture was diluted with CH_2Cl_2 (20 mL), washed with aq. $NaHCO_3$ (5 mL), dried, filtered, and concentrated *in vacuo*. Flashed chromatography on silicon gel gave the corresponding MTPA ester as colorless oil (19 mg, 0.0256 mmol, 75%, HE:AE/2:1, $R_f = 0.26$). ^1H NMR($CDCl_3$): 7.53-7.51 (m, 2H), 7.38-7.34 (m, 3H), 5.81-5.75 (m, 1H), 5.33-5.29 (m, 2H), 4.44 (dd, J = 12.4, 3.2 Hz, 1H), 4.26-4.18 (m, 4H), 4.09 (dd, J = 12.0, 7.2 Hz, 1H), 3.53 (s, 3H), 2.47-2.27 (m, 2H), 2.56 (t, J = 7.6 Hz, 2H), 1.98 (m, 4H), 1.55 (m, 2H), 1.36 (t, J = 6.8 Hz, 6H), 1.26 (m, 20H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.01 (s), 165.48 (s), 131.88 (s), 129.99 (s), 129.70 (s), 129.61 (s), 128.32 (s), 127.34 (s), 67.58 (m), 64.86 (d, J = 6.83 Hz), 64.35 (s), 55.37 (d, J = 1.51 Hz), 34.80 (td, J = 20.71, 15.38 Hz), 33.87 (s), 31.88 (s), 29.74 (s), 29.67 (s), 29.50 (s), 29.30 (s), 29.12 (s),

29.06 (s), 27.19 (s), 27.15 (s), 24.66 (s), 22.66 (s), 16.32 (d, J = 5.33 Hz), 14.08 (s). ^{19}F NMR($CDCl_3$): -72.07 (s), -112.10 (1F, dtd, J =103.86, 22.20, 16.93 Hz), -112.38 (1F, ddt, J = 103.86, 22.20, 16.93 Hz). ^{31}P NMR($CDCl_3$): 6.81 (t, J = 104.28 Hz).

II. Synthesis of Difluoro Analogs of LPA

Another approach to the synthesis of difluoromethylene analogs of LPA is depicted in Figure 5. Synthesis of the target LPA analogues **10a** and **10b** (Figure 5) involved non-reductive deprotection of the penultimate dimethyl phosphates **9** with trimethylsilane bromide to permit incorporation of unsaturated acyl chains. The key step for the synthesis was the introduction of the difluoromethyl group by the 1,1-difluorination of a C-1 aldehyde. Thus, commercially-available D-mannitol 1,2:5,6-bis-acetonide was oxidatively cleaved with $NaIO_4$ to afford the acetonide-protected D-glyceraldehyde **2**.10 Addition of (diethylamino)sulfur trifluoride (DAST) to a solution of the aldehyde **2** in CH_2Cl_2 afforded the difluorinated compounds in high yield after purification by distillation under reduced pressure.

Next, acidic cleavage of the acetonide-protecting group provided the diol intermediate **4**. The crude diol obtained after removal of the acetonide was immediately converted to the bis-silyl ether **5**, and the more labile TBDMS ether of the primary alcohol was cleaved selectively by treatment with a solution of pyridinium hydrofluoride in a mixture of pyridine and THF at rt. Initial attempts to obtain the primary alcohol **6** from bis-TBDMS ether **5**, utilizing 4.0 eq. of pyridinium hydrofluoride resulted in disappointing yields (17%) after 48 h at rt. However, increasing to 6.0 equiv. gave the primary alcohol in good yield (73%) after 20 h at rt. The primary alcohol **6** was then phosphorylated with dimethylphosphoryl chloride in the presence of *t*-BuOK to give good yield of phosphate **7**. The 2-TBDMS ether was further deprotected with tetra(*n*-butyl)ammonium fluoride (TBAF) in THF to give alcohol **8** in 72% yield; neutralization of TBAF with acetic acid permitted desilyation of the secondary alcohol without the migration of phosphate. DCC-promoted esterification of alcohol **8** with oleic acid or palmitic acid provided good yield of esters **9a** and **9b**, respectively. Importantly, the introduction of the acyl groups at this

stage circumvents problems with acyl group migration during other synthetic operations. Finally, treatment of protected phosphates **9** with bromotrimethylsilane and subsequent addition of 5% aq. methanol provided the desired difluorinated LPA analogues **10** in essentially quantitative yield.

General procedures. Chemicals were obtained from Aldrich and Acros and used without prior purification. Solvents were reagent-grade and distilled before use: THF was distilled from sodium wire, and CH_2Cl_2 was distilled from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. NMR spectra were recorded at 25 °C at 400 MHz (1H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F). Chemical shifts are given in ppm relative to tetramethylsilane as the internal standard for ^1H and ^{13}C spectra ($\delta = 0.00$); external standards were used for ^{31}P (85% H_3PO_4, $\delta = 0.00$) and ^{19}F ($CFCl_3$, $\delta = 0.00$).

(*R*)-Glyceraldehyde acetonide (2) was prepared from D-mannitol-1,2:5,6-bis-acetonide as described10 to give aldehyde **2** as a clear liquid: $[\alpha]^{20}_D$: + 64.4 (lit.19 $[\alpha]^{20}_D$ + 64.9).

(2*R*)-3,3-Difluoro-1,2-propanediol 1,2-acetonide (3). To a well-stirred solution of 8.10 g (62.3 mmol) of aldehyde **2** in dry CH_2Cl_2 (100 mL) was slowly added 10.2 mL (74.8 mmol) of DAST. After stirring 24 h at rt, the reaction mixture was quenched with 10% $NaHCO_3$ solution (80 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organics were dried (Na_2SO_4). The solvent was removed by fractional distillation until the head temperature reached 40 °C. The residue was then distilled at reduced pressure (ca. 24 mm Hg), collecting the fraction distilling at 65-66 °C to give 6.5 g (51.2 mmol, 83%) of difluoride **3** as a clear liquid. ^1H NMR (CDCl3): δ 5.68 (td, *J* = 56.0, 4.8 Hz, 1H), 4.23 (m, 1H), 4.10 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (CDCl3): δ 114.83 (t, *J* = 243.9 Hz), 111.19 (s), 74.83 (t, *J* = 27.6 Hz), 64.19 (dd, *J* = 5.3, 2.0Hz), 26.50 (s), 25.11 (s). 19F NMR (CDCl3): δ -127.02 (1F, ddd, 2*JFF* = 292.0, 2*JFH* = 54.0, 3*JFH* = 10.5 Hz), -129.82 (1F, ddd, 2*JFF* = 292.0, 2*JFH* = 54.0, 3*JFH* = 10.5 Hz). MS (CI) *m/z* 153.0 (M^++1, 100.00), 137.0 (M^+-CH_3, 6.56). HRMS, M^++1, Found: 153.0739. Calcd for

$C_6H_{11}O_2F_2$,153.0727. $[\alpha]^{20}_D$: -3.1 (1.09, MeOH).

(2*R*)-3,3-Difluoro-1,2-di{[1-(*t*-butyl)-1,1-dimethylsilyl]oxyl}-propane (5). To a solution of acetonide **3** (2.20 g, 14.47 mmol) in MeOH (30 mL) was added *p*TsOH (0.412 g, 2.17 mmol, 0.15 eq.) and the solution was stirred for 24 h at rt. After addition of NEt_3 (1 mL), the solvent was removed under reduced pressure. Next, crude diol **4** was dissolved in anhydrous DMF (16 mL) and stirred with imidazole (2.96 g, 43.41 mmol, 2.9 eq.) and *t*-butyldimethylsilyl chloride (TBSCl) (6.11 g, 40.52 mmol, 2.8 eq.) for 24 h at rt. The solution was diluted with water (60 mL) and ethyl acetate (100 mL), and the aqueous layer was separated and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified on silica gel (*n*-hexane-ethyl acetate 60:1, R_f = 0.36) to afford bis-TBDMS ether **5** as a colorless liquid 3.97 g (11.68 mmol, 81%). ^{1}H NMR ($CDCl_3$): δ 5.67 (td, *J* = 55.6, 4.0 Hz, 1H), 3.72 (m, 2H), 3.62 (m, 1H), 0.84 (s, 9H), 0.83 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.003 (s, 3H), 0.000 (s, 3H). ^{13}C NMR($CDCl_3$):δ 120.79 (t, *J* = 243.5 Hz), 78.26 (dd, *J* = 23.7, 21.4 Hz), 68.83 (t, *J* = 4.5 Hz), 31.40 (s), 31.24 (s), 23.86 (s), 23.73 (s), 0.76 (s), 0.58 (s), 0.03 (s), 0.00 (s). ^{19}F NMR ($CDCl_3$): δ -130.58 (1F, ddd, *J* (as above) = 284.1, 55.3, 5.3 Hz), -134.05 (1F, ddd, *J* = 284.1, 55.3, 5.3 Hz). MS (CI) *m/z* 314.2 (M^++1, 100.00), 283.1 (M+-C4H9, 10.42). HRMS, M^++1, Found: 341.2134. Calcd for $C_{15}H_{35}O_2F_2Si_2$, 341.2143. $[\alpha]^{20}_D$: -10.1 (0.61, MeOH).

(2*R*)-3,3-Difluoro-2-di[[1-(*t*-butyl)-1,1-dimethylsilyl]oxyl]-1-propanol (6). The HF-pyridine complex (70%, 30 mmol fluoride) was added to a mixture of pyridine (2.62 mL), and then a solution of bis-ether **5** (1.70 g, 5.00 mmol) in THF (25 mL) was added. The reaction mixture was stirred for 20 h at rt. After completion of the reaction (monitored by TLC), the solution was diluted with ethyl acetate (100 mL), washed with 0.5 M HCl (2 x 20 mL) and then with satd. $CuSO_4$ solution (20 mL), and dried (Na_2SO_4). After concentration *in vacuo*, the residue was purified on silica gel (*n*-hexane-ethyl acetate 5:1, R_f = 0.31) to afford 0.82 g of mono-ether **6** as a colorless liquid (3.63 mmol, 73%). ^{1}H NMR ($CDCl_3$): δ 5.58 (td, J = 53.6, 6.0 Hz, 1H), 3.68

(m, 2H), 3.59 (m, 1H), 1.79 (br, 1H), 0.79 (s, 9H), 0.00 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 120.05 (t, J = 234.5 Hz), 77.37 (dd, J = 27.6, 22.3 Hz), 67.21 (dd, J = 6.5, 3.0 Hz), 30.62 (s), 23.06 (s), 0.11 (s), 0.00 (s). ^{19}F NMR ($CDCl_3$): δ -128.55 (1F, ddd, J = 289.4, 55.3, 6.4 Hz), -130.25 (1F, ddd, *J* = 289.4, 55.3, 6.4 Hz). MS (CI) *m/z* 227.1 (M^++1, 100.00), 169.0 (M^+-C4H9, 8.11). HRMS, M^++1, Found: 227.1264. Calcd for $C_9H_{21}O_2F_2Si$, 227.1279. $[\alpha]^{20}_D$: -11.3 (0.79, MeOH).

(2*R*)-3,3-Difluoro-2-di[[1-(*t*-butyl)-1,1-dimethylsilyl]oxyl]-1-phospho-propane dimethyl ester (7). To a stirred solution of 128 mg (0.566 mmol) of ether **6** and dimethyl chlorophosphate (98 mg, 0.679 mmol, 1.2 eq.) in CH_2Cl_2 (10 mL) at 0 °C was added *t*-BuOK (89 mg, 0.792 mmol, 1.4 eq.). The mixture was stirred 2 h at rt and the reaction was complete as determined by TLC. The reaction was quenched by addition of satd. aq. NH_4Cl (5 mL), the mixture was stirred 10 min, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organics were dried (Na_2SO_4), concentrated, and purified on silica gel (*n*-hexane-ethyl acetate 3:2, R_f = 0.41) to afford 136 mg of phosphotriester **7** as a colorless liquid (0.407 mmol, 72%). ^{1}H NMR ($CDCl_3$): δ 5.88 (td, *J* = 53.2, 3.2 Hz, 1H), 4.38 (m, 2H), 3.83 (m, 1H), 3.73 (d, *J* = 0.8 Hz, 3H), 3.70 (d, *J* = 0.8 Hz, 3H), 0.81 (s, 9H), 0.002 (s, 3H), 0.000 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 118.80 (td, *J* = 234.2, 6.9 Hz), 81.75 (t, *J* = 22.2 Hz), 66.65 (dd, *J* = 8.5, 3.1 Hz), 60.21 (t, *J* = 6.54 Hz), 31.35 (s), 23.85 (s), 0.00 (s), -0.03 (s). ^{19}F NMR ($CDCl_3$): δ -131.75 (1F, ddd, *J* = 292.4, 54.6, 7.9 Hz), -134.1 (1F, ddd, *J* = 292.4, 54.6, 7.9 Hz). ^{31}P NMR ($CDCl_3$):δ 1.467 (s). MS (CI) *m/z* 335.0 (M^++1, 100.00), 276.9 (M^+-C4H10, 13.15). HRMS, M^++1, Found: 335.1258. Calcd for $C_{11}H_{26}F_2O_2PSi$, 335.1255. $[\alpha]^{20}_D$: -75.7 (0.504, MeOH).

(2*R*)-3,3-Difluoro-2-oleoyl-1-phospho-propane dimethyl ester (9a). A solution of TBDMS ether **7** (59 mg, 0.178 mmol) in THF (5 mL) was treated successively with acetic acid (41 μL, 0.706 mmol) and tetrabutylammoniumfluoride trihydrate (223 mg, 0.706 mmol) at rt. After stirring for 4 h, the reaction was complete (TLC), and the solvent removed *in vacuo* and the crude product was purified only by passing through a short silica gel bed (ethyl acetate , R_f = 0.48) and concentrated *in vacuo* to afford the

alcohol 8 as a colorless liquid. To the crude alcohol 8 was added 55 mg (62 μL, 0.194 mmol) of oleic acid in dry CH_2Cl_2 (2 mL) followed by dropwise addition of a solution of DCC (55 mg, 0.266 mmol) and DMAP (13 mg, 0.106 mmol) in dry CH_2Cl_2 (3 mL). The solution was stirred for 16 h at rt, filtered, concentrated *in vacuo*, and purified on silica gel (*n*-hexane-ethyl acetate 1:1, R_f = 0.26) to afford 71 mg of oleate **9a** as a waxy solid (0.146 mmol, 82%). ^{1}H NMR ($CDCl_3$): δ 5.86 (td, *J* = 54.8, 4.0 Hz, 1H), 5.28 (m, 2H), 5.15 (m, 1H), 4.20 (m, 2H), 3.73 (d, *J* = 4.4 Hz, 3H), 3.70 (d, *J* = 4.4 Hz, 3H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.93 (m, 4H), 1.58 (m, 2H), 1.22 (m, 20H), 0.81 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 172.52 (s), 130.25 (s), 129.90 (s), 112.72 (t, *J* = 244.6 Hz), 70.04 (td, *J* = 25.24, 7.64 Hz), 63.91 (d, *J* = 4.6 Hz), 54.76 (d, *J* = 6.1 Hz), 34.18 (s), 34.09 (s), 32.11 (s), 29.97 (s), 29.88 (s), 29.73 (s), 29.53 (s), 29.33 (s), 29.27 (s), 29.18 (s), 27.43 (s), 27.36 (s), 25.16 (s), 24.92 (s), 22.88 (s), 14.31 (s). ^{19}F NMR ($CDCl_3$): δ -130.101 (1F, ddd, *J* = 294.7, 53.8, 10.5 Hz), -131.0 (1F, ddd, *J* = 294.7, 53.8, 10.5 Hz). ^{31}P NMR ($CDCl_3$): δ 2.111 (s). MS (CI) *m/z* 485.3 (M^++1, 64.53), 359.2 (M^+-$C_2H_6PO_4$, 100.00). HRMS, M^++1, Found: 485.2867. Calcd for $C_{23}H_{44}F_2O_6P$, 485.2844. $[\alpha]^{20}_D$: -8.6 (1.08, MeOH).

(2*R*)-3,3-Difluoro-2-oleoyl-1-phospho-propane (10a). An aliquot of protected ester **9a** (55 mg, 0.114 mmol) was thoroughly dried (5 h, 1 μm Hg), dissolved in dry CH_2Cl_2 (2 mL) at rt, and then bromotrimethylsilane (53 μL, 0.398 mmol) was added dropwise with a dry syringe and the mixture was stirred for 4 h at rt. When TLC indicated that all of the reactant had disappeared, solvents were removed in vacuo, the residue was dissolved in 95% methanol (1 mL) for 1 h, and then reconcentrated *in vacuo* to give 50 mg of LPA 2-oleate analogue **10a** as a colorless oil (0.110 mmol, 96%) that was homogeneous by TLC: CH_2Cl_2/CH_3OH/H_2O, 20:10:1, R_f = 0.58. ^{1}H NMR (CD_3OD): δ 6.03 (t, *J* = 54.4 Hz, 1H), 5.53 (m, 2H), 5.24 (m, 1H), 4.18 (m, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.02 (m, 4H), 1.63 (m, 2H), 1.30 (m, 20H), 0.89 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): δ 173.70 (s), 130.88 (s), 130.78 (s), 114.43 (t, *J* = 242.4 Hz), 71.22 (td, *J* = 23.73, 8.45 Hz), 63.89 (d, *J* = 4.6 Hz), 34.67 (s), 33.06 (s), 30.84 (s), 30.78 (s), 30.61 (s), 30.44 (s), 30.34 (s), 30.26 (s), 30.16 (s), 30.04 (s),

28.12 (s), 25.84 (s), 23.73 (s), 14.15 (s). ^{19}F NMR (CD_3OD):δ -130.10 (1F, ddd, J = 295.8, 55.3, 9.4 Hz), -131.7 (1F, ddd, J = 295.8, 55.3, 9.4 Hz). ^{31}P NMR ($CDCl_3$): δ 0.742 (s). MS (CI) *m/z* 457.2 (M^++1, 13.75), 377.2 (M++2-H2PO3, 100.00). HRMS, M^++1, Found: 457.2535. Calcd for $C_{21}H_{40}F_2O_6P$, 457.2531. $[\alpha]^{20}_D$: -9.3 (1.02, MeOH).

(2*R*)-3,3-Difluoro-2-palmitoyl-1-phospho-propane dimethyl ester (9b). A solution of TBDMS ether **7** (59 mg, 0.178 mmol) in THF (5 mL) was treated successively with acetic acid (41 μL, 0.706 mmol) and tetrabutylammoniumfluoride trihydrate (223 mg, 0.706 mmol) and processed as described for **9a** to give crude alcohol **8**. The crude alcohol was directly esterified with 50 mg (0.194 mmol) of palmitic acid in dry CH_2Cl_2 (2 mL) at rt by dropwise addition of a solution of DCC (55 mg, 0.266 mmol) and DMAP (13 mg, 0.106 mmol) in dry CH_2Cl_2 (3 mL). The solution was stirred for 16 h at rt, filtered, concentrated *in vacuo*, and the residue was purified on silica gel (*n*-hexane/ethyl acetate 1:1, R_f = 0.36) to afford 62 mg of ester **9b** a waxy solid (0.136 mmol, 77%). ^{1}H NMR (CD_3OD): δ 6.05 (td, J = 54.8, 4.4 Hz, 1H), 5.30 (m, 1H), 4.29 (m, 2H), 3.80 (d, J = 5.2 Hz, 3H), 3.77 (d, J = 4.8 Hz, 3H), 2.42 (t, J = 7.6 Hz, 2H), 1.64 (m, 2H), 1.28 (m, 24H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (CD_3OD): δ 173.59 (s), 114.34 (t, J = 244.0 Hz), 71.11 (td, J = 25.34, 6.94 Hz), 65.39 (d, J = 5.3 Hz), 54.42 (d, J = 6.1 Hz), 34.76 (s), 34.65 (s), 33.08 (s), 30.78 (s), 30.69 (s), 30.57 (s), 30.48 (s), 30.37 (s), 30.04 (s), 26.76 (s), 26.05 (s), 25.86 (s), 23.73 (s), 14.44 (s). ^{19}F NMR (CD_3OD): δ -131.7 (1F, dt, J = 55.3, 10.5 Hz), -131.9 (1F, dt, J = 55.3, 10.5 Hz). ^{19}F NMR ($CDCl_3$): δ -130.1 (1F, ddd, J = 296.2, 55.3, 12.0 Hz), -131.0 (1F, ddd, J = 296.2, 55.3, 12.0 Hz). ^{31}P NMR (CD_3OD): δ 1.816 (s). MS (CI) m/z 459.3 (M^++1, 83.09), 333.2 (M^+-$C_2H_6PO_4$, 100.00). HRMS, M^++1, Found: 459.2708. Calcd for $C_{21}H_{42}F_2O_6P$, 4592687. $[\alpha]^{20}_D$: -10.3 (0.80, MeOH).

(2*R*)-3,3-Difluoro-2-oleoyl-1-phospho-propane (10b). As described for **10a**, thoroughly dried ester **9b** (38 mg, 0.083 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and deprotected with bromotrimethylsilane (38 μL, 0.290 mmol). The crude product was dissolved in 95% methanol (1 mL) for 1 h and reconcentrated and thoroughly

dried *in vacuo* to give 33 mg of LPA palmitate analogue **10b** (0.077 mmol, 93%). ^{1}H NMR (CD_3OD): δ 5.81 (td, J = 55.2, 4.4 Hz, 1H), 5.03 (m, 1H), 3.96 (m, 2H), 2.20 (t, J = 6.8 Hz, 2H), 1.41 (m, 2H), 1.07 (s, 24H), 0.68 (t, J = 6.8 Hz, 3H). ^{13}C NMR (CD_3OD): δ 173.72 (s), 114.43 (t, J = 242.3 Hz), 71.22 (td, J = 23.73, 8.45 Hz), 63.92 (d, J = 4.6 Hz), 34.68 (s), 33.08 (s), 30.79 (s), 30.77 (s), 30.72 (s), 30.58 (s), 30.48 (s), 30.39 (s), 30.07 (s), 25.86 (s), 23.74 (s), 14.46 (s). ^{19}F NMR (CD_3OD):-132.08 (1F, ddd, J = 295.4, 54.2, 9.4 Hz), -132.7 (1F, ddd, J = 295.4, 54.2, 9.4 Hz). ^{31}P NMR (CD_3OD): 0.709 (s). MS (CI) *m/z* 431.1 (M^++1, 3.39), 333.1 (M^+-H2PO4, 100.00). HRMS, M^++1, Found: 431.2369. Calcd for $C_{19}H_{38}F_2O_6P$, 431.2375. $[\alpha]^{20}_D$: -2.1 (0.90, MeOH).

(2*R*)-3,3-Difluoro-2-*O*-[(S)-α-methoxy-α-(trifluoromethyl)phenylacetyl]-1-phospho-propane dimethyl ester (11). A solution of alcohol **8** and (*R*)-methoxy-(trifluoromethyl)phenylacetic acid chloride in pyridine was stirred for 20 h at rt. The mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$, dried, filtered, and concentrated. Flash chromatography on silica gel gave the corresponding MTPA ester as colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.52 (m, 2H), 7.40 (m, 3H), 5.87 (td, J = 54.4, 4.0 Hz, 1H), 5.47 (m, 1H), 4.40 (m, 1H), 4.28 (m, 1H), 3.72 (d, J = 8.0 Hz, 3H), 3.75 (d, J = 8.0 Hz, 3H), 3.55 (m, 3H). ^{19}F NMR ($CDCl_3$): -72.36 (s), -129.37 (1F, ddd, J = 296.2, 55.3, 11.0 Hz), -130.27 (1F, ddd, J = 296.2, 55.3, 11.0 Hz); -72.17 (1.59), -72.36 (98.41), > 97% ee. ^{31}P NMR ($CDCl_3$):δ 1.728 (s).

III. Synthesis of Hydroxyethoxy Susbstituted Analogs of LPA

In the routes leading to *syn*-1 HE-LPA analogs (Figure 6), the regiospecific and stereospecific ring opening of (S)-glycidol with 4-methoxybenzyl (PMB) alcohol by diisobutylaluminium hydride (DIBAL), generated the PMB protected glycerol (**1-1**). Using 4-(dimethylamino) pyridine (DMAP) as the catalyst, the primary alcohol of the diol was selectively silylated over the secondary alcohol by *t*-butyldimethylsilyl chloride in 78% yield. Initial attempts to obtain (**1-3**) from the secondary alcohol (**1-2**), using 2(2-bromoethoxy) tetrahydro-2-H-pyran in the presence of NaH in anhydrous DMF, resulted in no product after 48 h at room temperarture. However

adding tetrabutylammonium iodide (TBAI) into the reaction gave the alkylated product in 56% yield after 18 h at room temperarture. Then the 1-TBDMS ether was deprotected with tetra(n-butyl)ammonium fluoride (TBAF) in THF to give alcohol (**1-4**), which was esterified with oleic acid or palmitic acid using DCC and DMAP to produce good yields of esters (**1-5a**) and (**1-5b**), respectively. Oxidative removal of the PMB groups with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) produced corresponding alcohols (**1-6a**) and (**1-6b**). They were then phosphorylated with dimethyl chlorophosphate in the presence of *t*-BuOK to give good yields of phosphates (**1-7a**) and (**1-7b**). The non-reductive deprotection of dimethyl phosphates with bromotrimethylsilane was compatible with the unsaturated acyl chains. The trace of acid generated during workup (adding MeOH/H_2O) resulted in elimination of tetrahydropyranyl groups (THP) and generation of our target compounds (**1-8a**) and (**1-8b**).

The strategies for the synthesis of non-migrating *sn*-2 HE-LPA analogs were similar to those used for the preparation of *sn*-1 HE-LPA (Figure 7). In order to get (2S) enantiomer of the sn-2 HE-LPA analogs, (R)-Glycidol was used. After the regiospecific and stereospecific ring opening of Glycidol and TBDMS protection of the diol, the selective deprotection of bis-TBDMS ether (**2-2**) utilizing 6.0 eq. of pyridinium hydrofluoride (HF-Py / Py), resulted in 58% yield after 18 h at room temperarture. The amount of HF-Py was crucial to the reaction since more would cause deprotection of both TBDMS groups and less amount would lead to low yields. Interestingly, phosphorylation of (**2-3**) using mtheylimidazole instead of *t*-BuOK increased the yield from 10% to 87%. The 2-TBDMS ether was further deprotected with TBAF.$3H_2O$ in THF to give alcohol (**2-5**); neutralization of TBAF with acetic acid allowed the desilyation of the secondary alcohol without the migration of phosphate. After DCC-promoted esterification and TMSBr deprotection, *syn*-2 LPA analogs (**2-7a**) and (**2-7b**) were obtained in good yields.

The enantiomeric purity of (**1-2**) and (**2-5**) was determined by Mosher's ester method, and optical purities were measured by integration of the ^{1}H-NMR.

General Procedures. Chemicals were purchased from Aldrich and Acros Chemical Corporation and used without prior purification. Solvents were reagent-grade and distilled before use: CH_2Cl_2 was distilled from CaH_2 and THF was distilled from sodium wire. TLC: precoated silica) gel aluminum sheets (EM SCIENCE silica gel $60F_{254}$). Flash Chromatography (FC): Silica gel Whatman 230~400 mesh astm. NMR spectra were recorded on a Varian INOVA 400 at 400 MHz (^1H), 101 MHZ (^{13}C), 162 MHz (^{31}P) at 25°C. Chemical shifts are given in ppm with TMS as internal standard (δ=0.00); ^{31}P, 85% H_3PO_4 (δ=0.00).

3-*O*-Methoxybenzyl-*sn*-glycerol (1-1). To a solution of PMBOH (9.8 g, 70 mmol) in 25ml anhydrous CH_2Cl_2 in an ice bath, 1.0M DIBAL-H in Hexane (30 mL) was added. The reaction mixture was warmed to rt and stirred for 0.5 h. (S)-Glycidol (2 mL, 30 mmol) was added to the reaction mixture which was then stirred at rt for 70 h. Sodium potassium tartrate (6.3 g, 30 mmol) in a minimum amount of water was then added to the mixture and stirring continued for 0.5 h. The solvent was evaporated and the mixture was extracted with ethyl acetate, washed with water, dried over sodium sulfate, and concentrated. The crude product was purified by flash chromatography (EtOAc) to afford colorless oil 3.3g (51%). R_f 0.28 (EtOAc); ^1H-NMR ($CDCl_3$) δ 3.517 (m, 2H), 3.599 (dd, 1H, J=11.2, 5.4 Hz), 3.5678 (dd, 1H, J=11.2, 3.4 Hz), 3.798 (s, 3H), 3.862 (m, 1H), 4.472 (s, 2H), 6.878 (dd, J=8.4, 2.0 Hz), 7.242 (dd, J=8.0, 2.4 Hz); ^{13}C-NMR, δ 55.253, 64.054, 70.574, 71.474, 73.220, 113.875, 129.440, 129.722, 159.372; MS (FAB) m/z 235 (M^++Na, 24). HRMS, M^++Na, Found:235.0939, Calcd for $C_{11}H_{16}O_4Na$, 235.0946.

3-*O*-*tert*-butyl-dimethysily-1-*O*-Methoxybenzyl-*sn*-glycerol (1-2). A mixture of **1-1** (950 mg, 4.48 mmol), tert-butyldimethylsilyl chloride (810 mg, 5.4 mmol), TEA (546 mg, 5.4 mmol) and DMAP (55 mg, 0.448 mmol) in anhydrous CH_2Cl_2 (15 mL) under an argon atmosphere was stirred at rt for 18 h. The reaction mixture was washed with NaCl saturated solution, dried over Na_2SO_4, and concentrated. FC (EtOAc/Hexane, 1/4, v/v) gave **1-2** as a colorless oil 980mg (78%). R_f 0.31 (EtOAc/Hexane 1/4); ^1H-NMR ($CDCl_3$, 400MHz) δ 0.0 (s, 6H), 0.828 (s, 9H), 3.430 (m, 2H), 3.579 (m, 2H),

3.737 (s, 3H), 3.782 (m, 1H), 4.417 (s, 2H), 6.815 (dd, J=8.8, 2.0Hz), 7.192 (dd, J=8.8, 2.0Hz); ^{13}C-NMR, δ -5.457, 18.237, 25.825, 55.208, 63.993, 70.628, 70.643, 73.045, 113.761, 129.333, 130.126, 159.228; MS (FAB) m/z 325 (M^++H, 7). HRMS, M^++H, Found: 325.1831, Calcd for $C_{17}H_{29}O_4Si$, 325.1835.

3-*O*-*tert*-butyl-dimethysily-1-*O*-Methoxybenzyl-2-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (1-3). To a solution of **2** (900 mg, 2.76 mmol) in dry DMF (25 mL) was added 60% NaH in oil dispersion (375 mg, 9.4 mmol). The mixture was stirred at rt for 0.5 h. The bromide (1.25 ml, 8.28 mmol) and TBAI (1 g, 2.76 mmol) was added to the reaction. The mixture was stirred at rt for 18 h. After adding 5ml H_2O, the solvent was evaporated. The mixture was extracted with EtOAc (20 mL × 3). The extract was washed with NaCl saturated solution, dried over Na_2SO_4, and concentrated. FC (EtOAc/Hexane, 1/4, v/v) gave **1-3** as a colorless oil mg (56%). R_f 0.35 (EtOAc/Hexane 1/4); ^{1}H-NMR ($CDCl_3$) δ 0.004 (s, 6H), 0.841 (s, 9H), 1.513 (m, 4H), 1.718 (m, 2H), 3.450 (m, 2H), 3.531 (m, 2H), 3.624 (m, 2H), 3.724~3.754 (m, 1H), 3.759 (s, 3H), 3.802 (m, 2H), 4.44 (d, 2H, J=2.4Hz), 4.586 (t, 1H, J=3.6Hz), 6.824 (dd, J =8.4, 1.6Hz), 7.195(dd, J=8.4, 1.6Hz); ^{13}C-NMR, δ -5.423, -5.377, 18.264, 19.431, 25.455, 25.875, 30.572, 55.258, 62.083, 62.114, 62.579 (d, J=7.68Hz), 66.956 (d, J=7.68Hz), 69.809 (d, J=6.16Hz), 80.149 (d, J=7.68Hz), 98.856 (d, J=7.68Hz), 113.704, 113.818, 129.215, 129.360, 130.558, 159.102; MS (FAB) m/z 477 (M^++Na, 17). HRMS, M^++Na, Found: 477.2629, Calcd for $C_{24}H_{42}O_6NaSi$, 477.2648.

3-*O*-Methoxybenzyl-2-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (1-4). To a solution of **1-3** (330 mg, 0.726 mmol) in THF (5 mL) was added 1M TBAF in THF (1.45 mL). The reaction mixture was stirred at rt for 3 h. The mixture was washed with NaCl saturated solution, dried over Na_2SO_4, and concentrated. FC (EtOAc/Hexane, 3/1, v/v) gave **1-4** as a colorless oil 241 mg (95%). R_f 0.22 (EtOAc/Hexane 3/2); ^{1}H-NMR ($CDCl_3$) δ 1.550 (m, 4H), 1.762 (m, 2H), 2.5 (br, 1H), 3.474~3.743 (m, 7H), 3.805 (s, 3H), 3.858 (m, 2H), 4.464 (s, 2H), 4.637 (m, 1H), 6.876 (dd, J =7.6, 2.0Hz), 7.251 (dd, J=7.6, 2.0Hz); ^{13}C-NMR, 19.393 (d, J=3.13Hz),

25.287, 30.466 (d, J=7.78Hz), 55.243, 62.335 (d, J=4.65Hz), 62.838 (d, J=12.32Hz), 67.132 (d, J=18.48Hz), 69.824, 69.9 (d, J=4.65Hz), 73.118, 79.745, 99.013 (d, J=10Hz), 113.78, 129.254, 129.383, 130.115, 159.224; MS (FAB) m/z 363 (M^++Na, 33). HRMS, M^++Na, Found: 363.1769, Calcd for $C_{18}H_{28}O_6Na$, 363.1784.

1-*O*-Methoxybenzyl-3-*O*-Oleoyl-2-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (1-5a). A solution of **1-4** (240 mg, 0.705 mmol), oleic acid (319 mg, 1.13mmol), DCC (233 mg, 1.13mmol), DMAP (40 mg, 0.141 mmol) in CH_2Cl_2 (10ml) was stirred at rt for 18 h, filtered through Celite, and concentrated. FC (EtOAc/Hexane, 1/4, v/v) gave **1-5a** as a colorless oil 350 mg (82%). R_f 0.26 (EtOAc/Hexane 1/4) ^{1}H-NMR ($CDCl_3$). δ 0.874 (t, J=6.8Hz, 3H), 1.275 (m, 20H), 1.4~1.8 (m, 8H), 2.002 (m, 2H), 2.284 (t, J=7.6Hz, 2H), 3.45~3.85 (m, 7H), 3.796 (s, 3H), 4.2 (m, 2H), 4.472 (s, 2H), 4.619 (m, 1H), 5.336 (m, 2H), 6.854 (dd, J =8.8, 2.0Hz), 7.237 (dd, J=8.8, 2.0Hz) ; ^{13}C-NMR,; MS (FAB) m/z 627 (M^++Na, 43). HRMS, M^++Na, Found: 627.4203, Calcd for $C_{36}H_{60}O_7Na$, 627.4237.

3-*O*-Oleoyl-2-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (1-6a). A solution of **1-5a** (340 mg, 0.562 mmol), DDQ (128 mg, 0.562 mmol) in wet CH_2Cl_2 (10 mL) was stirred at rt for 8 h. After filtration, the filtrate was washed with NaCl saturated solution, dried over Na_2SO_4, and concentrated. FC (EtOAc/Hexane, 2/3, v/v) gave **1-6a** as a colorless oil 180 mg (66%). R_f 0.36 (EtOAc/Hexane 1/1); ^{1}H-NMR ($CDCl_3$, 400MHz), δ 0.877 (t, J=7.2Hz, 3H), 1.273 (m, 20H), 1.52~1.804 (m, 8H), 2.006 (m, 2H), 2.319 (t, J=7.2Hz, 2H), 3.50~3.76 (m, 6H), 3.92 (m, 3H), 4.13 (m, 2H), 4.65 (m, 1H), 5.34 (m, 2H); MS (FAB) m/z 507 (M^++Na, 95). HRMS, M^++Na, Found: 507.3665, Calcd for $C_{28}H_{52}O_6Na$, 507.3662.

3-*O*-dimethylphosphoryl-1-*O*-Oleoyl-2-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (1-7a). To a solution of **6** (55 mg, 0.113 mmol) in CH_2Cl_2 (5 mL) in an ice bath was added $(OMe)_2POCl$ (20 mg, 0.136 mmol), *t*-BuOK (19 mg, 0.17 mmol). The reaction mixture was stirred at rt for 2 h. NH_4Cl saturated solution (2 mL) was added and the mixture was stirred for 10 min. The reaction mixture was extracted with CH_2Cl_2, the extract was washed with NaCl saturated solution, dried over Na_2SO_4,

and concentrated. FC (EtOAc/Hexane, 2/1, v/v) gave **1-7a** as a colorless oil 50 mg (75%). R_f 0.26 (EtOAc/Hexane 2/1); ^{1}H-NMR ($CDCl_3$, 400MHz), δ 0.875 (t, J=6.8Hz, 3H), 1.280 (m, 20H), 1.499~1.819 (m, 8H), 2.004 (m, 2H), 2.32 (t, J=8Hz, 2H), 3.529 (m, 2H), 3.71~3.872 (m, 11H), 4.128 (m,2H), 4.247 (m, 2H), 4.62 (t, J=4.4, 1H), 5.34 (m, 2H); MS (FAB) m/z 615 (M^++Na, 100). HRMS, M^++Na, Found: 615.3646, Calcd for $C_{30}H_{57}O_9NaP$, 615.3638.

2-*O*-hydroxyethyl-1-*O*-oleoyl-3-*O*-phosphoryl-*sn*-glycerol (1-8a). A solution of **1-7a** (35 mg, 0.069 mmol), TMSBr (37 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 5 h. The solvent was evaporated and the residue was dissolved in 95% methanol (1 mL) stirring for 1h. Reconcentration of the solvent gave **1-8a** as a colorless oil 32 mg (95%). R_f 0.36 (CH_2Cl_2/MeOH/H_2O, 20/10/1); ^{1}H-NMR (CD_3OD), δ 0.893 (t, J=7.2Hz, 3H), 1.304 (m, 20H), 1.609 (m, 2H), 2.024 (m, 4H), 2.341 (t, J=7.6Hz, 2H), 3.667 (m, 4H), 3.787 (m, 1H), 4.049 (m,2H), 4.2 (m, 2H), 5.336 (m, 2H); ^{13}C-NMR (CD_3OD), δ 14.452, 23.74, 25.990, 28.125, 30.192, 30.299, 30.337, 30.444, 30.611, 30.81, 30.840, 33.059, 34.912, 62.42, 63.914, 66.56 (d, J=5.35Hz), 72.974, 77.985 (d, J=7.78Hz), 130.795, 130.894, 175.163. ^{31}P-NMR (CD_3OD), δ 1.078 (s).

2-*O*-hydroxyethyl-1-*O*-palmitoyl-3-*O*-phosphoryl-*sn*-glycerol (1-8b). R_f 0.36 (CH_2Cl_2/MeOH/H_2O, 20/10/1); ^{1}H-NMR (CD_3OD), δ 0.891 (t, J=7.2Hz, 3H), 1.281 (s, 24H), 1.608 (m, 2H), 2.34 (t, J=7.2Hz, 2H), 3.670 (m, 4H), 3.799 (m, 1H), 4.054 (m, 2H), 4.2 (m, 2H); ^{13}C-NMR, δ; ^{31}P-NMR, δ 1.078 (s)

3-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (2-1). R_f 0.25 (EtOAc); ^{1}H-NMR ($CDCl_3$) δ 1.521 (m, 4H), 1.78 (m, 2H), 2.710 (s, 1H), 3.332 (s, 1H), 3.51 (m, 2H), 3.56~3.70 (m, 6H), 3.857 (m, 3H), 4.610 (t, J=4 Hz, 1H); ^{13}C-NMR, δ 19.508 (d, J=1.15Hz), 25.299, 30.523, 62.503 (d, J=3.8Hz), 63.975 (d, J=2.2Hz), 66.732 (d, J=4.6Hz), 70.423 (d, J=3.0Hz), 70.846 (d, J=5.4Hz), 73.016 (d, J=7.6Hz), 99.166 (d, J=4.5Hz).

1,2-di-*O*-*tert*-butyl-dimethysilyl-3-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (2-2). A mixture of **2-1** (400 mg, 1.8 mmol), tert-butyldimethylsilyl chloride (663 mg, 4.4 mmol) and imidazole (272 mg, 4 mmol) in anhydrous DMF (6 mL) under an

argon atmosphere was stirred at rt for 20 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. FC (EtOAc/Hexane, 1/8, v/v) gave **2-2** as a colorless oil 730mg (91%). R_f 0.43 (EtOAc/Hexane 1/8); ^{1}H-NMR ($CDCl_3$) δ 0.068 (m, 12H), 0.883 (m, 18H), 1.483~1.856 (m, 6H), 3.423 (m, 2H), 3.48~3.65 (m, 6H), 3.839 (m, 3H), 4.632 (t, J=3.6 Hz, 1H); ^{13}C-NMR, δ -5.436, -5.375, -4.681, -4.635, 18.190, 18.335, 19.319, 19.380, 25.458, 25.831, 25.862, 25.946, 30.545 (d, J=1.5Hz), 62.010 (d, J=9.1Hz), 65.167, 65.949 (d, J=4.6Hz), 70.745 (d, J=5.4Hz), 72.709, 73.334 (d, J=3.0Hz), 98.866 (d, J=12.2Hz).

2-*O*-*tert*-butyl-dimethysilyl-3-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-glycerol (2-3). The HF-pyridine complex (0.383 mL, 13.2 mmol) was added to a mixture of **2-2** (1.0 g, 2.2 mmol) and pyridine (1.15 mL) in anhydrous THF (10 mL). After stirring 20 h at rt, the solution was diluted with EtOAc (50 mL), washed with 0.5M HCl (2 × 10 mL) and satd. $CuSO_4$ solution (10 mL). The organic layer was dried over Na_2SO_4, and concentrated. FC (EtOAc/Hexane, 1/2, v/v) gave **2-3** as a colorless oil 450mg (58%). R_f 0.35 (EtOAc/Hexane 1/2); ^{1}H-NMR ($CDCl_3$) 0.078 (s, 6H), 0.876 (s, 9H), 1.474~1.848 (m, 6H), 2.321 (t, J=3.6Hz, 1H), 3.455~3.645 (m, 8H), 3.872 (m, 3H), 4.609 (t, J=3.2 Hz, 1H); ^{13}C-NMR, δ -4.901, -4.665, 18.076, 19.319, 19.365, 25.367, 25.763, 30.468, 62.125 (d, J=6.1Hz), 65.041 (d, J=3.8Hz), 66.510 (d, J=6.1Hz), 70.711 (d, J=4.6Hz), 71.039 (d, J=3.0Hz), 73.194 (d, J=8.3Hz), 98.905 (d, J=10.7Hz).

1-*O*-(tetrahydro-pyran-2-yloxy)ethyl-2-*O*-*tert*-butyl-dimethysilyl-3-*O*-dimethylphosphoryl-*sn*-glycerol (2-4). Colorless oil. R_f 0.35 (EtOAc/Hexane 2/1); ^{1}H-NMR ($CDCl_3$) 0.073 (d, J=2.4Hz, 6H), 0.866 (s, 9H), 1.478~1.829 (m, 6H), 3.542 (m, 4H), 3.62 (m, 2H), 3.733 (s, 3H), 3.764 (s, 3H), 3.835 (m, 2H), 3.967 (m, 2H), 4.077 (m, 1H), 4.601 (t, J=4.0 Hz, 1H); ^{13}C-NMR, δ -4.874, -4.820, 18.058, 19.347, 19.385, 25.379, 25.684, 30.496, 54.183, 54.244, 62.103 (d, J=5.3Hz), 65.610 (d, J=2.3Hz), 69.008 (d, J=6.1Hz), 70.761 (dd, J=8.4, 2.3Hz), 70.850 (d, J=2.3Hz), 72.264 (d, J=4.6Hz), 98.906 (d, J=6.9Hz); ^{31}P-NMR, δ 2.379 (s).

3-*O*-dimethylphosphoryl-(2R)-*O*-oleoyl-1-*O*-(tetrahydro-pyran-2-yloxy)ethyl-*sn*-

glycerol (2-6a). R_f 0.50 (EtOAc); ^{1}H-NMR ($CDCl_3$) δ 0.871 (t, J=6.8Hz, 3H), 1.275 (m, 20H), 1.494~1.832 (m, 8H), 2.004 (m, 2H), 2.328 (t, J=7.2Hz, 2H), 3.542 (m, 4H), 3.579 (m, 2H), 3.664 (m, 6H), 3.858 (m, 2H), 4.223 (m, 2H), 4.611 (t, J=4.0Hz, 1H), 5.171 (m, 1H), 5.334 (m, 2H); ^{13}C-NMR, δ 14.083, 19.406, 22.655, 24.836, 25.393, 27.147, 27.193, 29.053, 29.091, 29.168, 29.297, 29.496, 29.686, 29.740, 30.525, 31.875, 34.231, 54.326, 54.387, 62.158, 65.983 (d, J=5.3Hz), 66.551, 68.808, 70.486, 70.562, 70.882, 98.912 (d, J=3.8Hz), 129.695, 129.992; ^{31}P-NMR, δ 2.258 (s)

1-*O*-hydroxyethyl-2-*O*-oleoyl-3-*O*-phosphoryl-*sn*-glycerol (2-7a). R_f 0.35 (CH_2Cl_2/MeOH/H_2O, 20/10/1); ^{1}H-NMR (CD_3OD) δ 0.893 (t, J=6.8Hz, 3H), 1.305 (m, 20H), 1.614 (t, J=6.8Hz, 2H), 2.024 (m, 4H), 2.347 (t, J=5.6Hz), 3.555 (m, 2H), 3.645 (t, J=4.4Hz, 2H), 3.708 (m, 2H), 4.14 (m, 2H), 5.145 (m, 1H), 5.337 (t, J=4.8Hz, 2H); ^{13}C-NMR, δ 13.260, 22.548, 24.775, 26.993, 28.954, 29.000, 29.153, 29.252, 29.419, 29.633, 29.656, 31.867, 33.865, 60.968, 64.698, 68.762, 71.252 (d, J=8.4Hz), 72.796, 72.850, 129.610, 129.694; ^{31}P-NMR, δ 1.012 (s).

1-*O*-hydroxyethyl-2-*O*-palmitoyl-3-*O*-phosphoryl-*sn*-glycerol (2-7b). R_f 0.35 (CH_2Cl_2/MeOH/H_2O, 20/10/1); ^{1}H-NMR (CD_3OD) δ 0.890 (t, J=6.8Hz, 3H), 1.280 (s, 24H), 1.601 (m, 2H), 2.346 (t, J=7.6Hz, 2H), 2.567 (m, 2H), 3.634 (m, 2H), 3.717 (m, 2H), 4.143 (m, 2H), 5.147 (m, 1H); ^{13}C-NMR, δ 14.431, 23.727, 25.969, 26.023, 30.156, 30.362, 30.423, 30.469, 30.560, 30.598, 30.675, 30.751, 30.781, 62.155, 65.937, 70.048, 72.801, 73.853, 74.010 (d, J=5.3Hz); ^{31}P-NMR, δ 0.957 (s).

IV. Synthesis of α-Fluorinated Phosphonates

One approach toward the target α-monofluorophosphonates involved the Wadsworth-Emmons condensation of carbanion, derived from tetraalkyl monofluoromethylenediphosphonates, with (*R*)-1,4-dioxaspiro[4,5]decane-2-carbaldehyde. The cyclohexyl protecting group in the aldehyde increased the stereoselectivity of condensation because the preferred conformation of vinylphosphonate had the most bulky β-carbon substituent *trans* to the phosphoryl group. The use of Selectfluor(1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane

bis(tetrafluoroborate), F-TEDA-BF_4) (Lal, *J. Org. Chem.*, 1993, 57, 4676-4683; Lal *et al. Chem. Rev.* 1996, 96, 1737-1755) was selected in the synthesis of tetraethyl fluoromethylenebisphosphonate. The tetraethyl methylenebisphosphonate was treated with sodium hydride, and the enolate was quenched with Selectfluor to give the tetraethyl fluoromethylenebisphosphonate **2** in good yield (52%).

Treatment of compound **2** with *n*-butyl lithium at -78 °C generated the lithiated carbonion, which condenses smoothly with aldehyde **3** giving good yield of the α-fluorovinylphosphonate (Figure 8). The condensation reaction showed a good stereoselectivity and gave a mixture of (*E*)- and (*Z*)-isomers in a 12:1 (mol ratio). Moreover, these two isomers can be separated easily by flash chromatograph. Their stereochemistry were confidently assigned on the basis of the $^3J_{PH}$ and $^3J_{HF}$ coupling constants for the alkene.

Catalytic hydrogenation of the alkene **4**, proceeded readily and quantitatively to give the corresponding α-fluoroalkylphosphonate **5** without loss of fluorine (Figure 8). The hydrogenation was carried out at ambient temperature and pressure using 10% Pd-C in absolute ethanol. Hydrolysis **5** using catalytic amount of *p*-toluenesulfonic acid in MeOH cleaved the acetonide protecting group readily. DCC-promoted esterification of diol **6** with palmatic acid, oleic acid or linoleic acid provided good yield of ester **7a**, **7b** and **7c**, respectively. Finally, treatment **7** with bromotrimethylsilane and subsequent addition of aqueous methanol (5%, H_2O) provided the desired fluorinated lysophosphatidic acid **8** in nearly quantitative yield.

The study on the LPA receptors/ligand interactions indicated introduction of *sn*-2 *O*-methyl group decreasing the ability to activate Edg4/LPA_2 receptor and increasing the Edg7/LPA_3 receptor subtype selectivity. For example, OMPT, a phospothionate analogue of LPA, exhibits preferred selectivity for Edg7/LPA_3 as compared to Edg2/LPA_1 or Edg4/LPA_2. In addition, selective introduction of *O*-methyl group at the *sn*-1 position can generate stable (acyl migration blocked) 2-acyl LPA analogues, which are a kind of important LPA species (Xu *et al. Clinical Cancer Research* 1995, 1, 1223-1232). In order to increase the subtype selectivity of analogs

8, the introduction of an *O*-methyl group at the *sn*-2 and *sn*-1 position was performed.

Selective introduction of a TBS protecting group at the *sn*-1 position of **6** was achieved by using 1.05 equivalent of TBSCl to produce **9** (Figure 9). Next, the use of Meerwein's trimethyloxonium tetrafluoroborate salts $(CH_3)_3O^+BF_4^-$ in conjunction with nonnucleophilic amine base (proton sponge, 1,8-bis(dimethylamino)naphthalene) gave a medium yield (43%) of methyl ether **10** after 14 days together with unreacted starting material. Alternatively, the reaction of trimethyloxonium tetrafluoroborate salts $(CH_3)_3O^+BF_4^-$ with diol **6** in the presence of proton sponge provided good yield of 1-*O*-methylation product **11** after 4 days reaction at room temperature (Figure 9). After esterification at *sn*-2 position and deprotection of diethyl ester, the acyl-chain migration-blocked *sn*-2 LPA analogues **13** were obtained.

Another approach to compound **10** involves the use of trimethylsilyldiazomethane $TMSCHN_2$, which smoothly reacts with alcohol **9** in dichloromethane in the presence of 42% aqueous fluoroboric acid (FBA) to give the corresponding methyl ether **10** in good yield. The stable TBDMS ether **10** was deprotected with *tetra*-(*n*-butyl)ammonium fluoride (TBAF) in THF to give the primary alcohol **14** (Figure 10); neutralization of TBAF with acetic acid inhibited the side-effect of basic medium. DCC-promoted esterification of **14** with either oleic acid or palmatic acid provided good yields of esters **15**. Finally, treatment of each ester **15** with bromotrimethylsilane and subsequent addition of 5% aq. methanol provided the desired *sn*-2 *O*-methylation LPA analogues **16** in nearly quantitatively yield. Moreover, the excessive TMSBr did not cleave off *O*-methyl ether.

Trimethylsilyldiazomethane $TMSCHN_2$ reacted with alcohol **9** smoothly to give methyl ether **10**. Using a similar approach, it was possible to go directly from alcohol **7** to compound **15**. The reaction of trimethylsilyldiazomethane $TMSCHN_2$ with alcohol **7** provided good yield of **15** and no migration of acyl chain was observed (Figure 10). This method not only saved several steps for the synthesis of *sn*-2 *O*-methylation LPA analogs, but also provided a new and concise synthetic route for the construction of this kind of compound.

General Procedure. Chemicals were obtained from Aldrich and Acros Chemical Corporation and were used without prior purification. Solvents used were of reagent grade and were distilled before use: THF was distillated from sodium wire. Methylene chloride was distillated from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. ^1H and ^{13}C spectra were recorded on 400 MHz (^1H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F), temp. 25°C. Chemical shifts are given in ppm with TMS as internal standard (δ=0.00); ^{31}P, 85% H_3PO_4 (δ=0.00); ^{19}F, $CFCl_3$ (δ=0.00). (*R*)-1,4-Dioxaspiro[4,5]decane-2-carbaldehyde was prepared from 1,2:5,6-Di-O-cyclohexylidene-D-mannitol according to Schick's method. (Schrotter, E.; Luong, T. T.; Schick, H. *J. Prakt. Chemie.* **1990**, *332*, 191-197).

Tetraethyl fluoromethylenebisphosphonate 2. NaH (0.641 g, 16.03 mmol, 60% in mineral oil) in a flame-dried flask under Ar was washed with Et_2O, and dried THF (90 mL) was added. The suspension was cooled (~0°C, ice bath), and compound **2** (4.40 g, 15.26 mmol) in THF (10 mL) was added. The solution was stirred (0°C for 15 min, ambient temperature for 60 min, cooled to 0°C), and selectfluor (6.76 g, 19.08 mmol) was added in one portion. After 15 min, dried DMF (35 mL) was added, the ice-bath was removed after 5 min, and stirring was continued at ambient temperature for 2 h. The reaction mixture was cooled to 0°C, and CH_2Cl_2 (40 mL) and saturated NH_4Cl/H_2O (40 mL) were slowly added. After 5 min, the organic layer was separated, and the aqueous layer was extracted (CH_2Cl_2). The combined organic phase was washed (saturated $NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and chromatographed(Ethyl acetate/CH_3OH:100/3, R_f = 0.54, 2.40 g, 7.84 mmol, 52% yield). ^1H NMR($CDCl_3$): 4.93 (dt, J = 46.0, 13.6 Hz,1H), 4.20 (m, 8H), 1.29 (t, J = 7.2 Hz, 12H). ^{19}F NMR($CDCl_3$): -288.26 (td, J = 62.9, 45.9 Hz, 1F). ^{31}P NMR($CDCl_3$): 12.20 (d, J = 63.0 Hz).

(*E*)-(3*R*)-Diethyl 1-Fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-enylphosphonate 4a. Treatment of tetraethyl fluoromethylenebisphosphonate (0.184 mg, 0.601 mmol in 5 mL dry hexane) with n-BuLi (0.601 mL, 1.0 M solution in hexane) at -78°C under dry nitrogen gas followed by addition of (*R*)-1,4-dioxaspiro[4,5]decane-2-carbaldehyde (0.143 g, 0.841 mmol) with stirring at -78°C gave a mixture which was brought to room temperature slowly. Filtration and evaporation under reduced temperature, followed by chromatograph (Ethyl acetate/hexane: 3/2) gave two isomers **4a** (R_f = 0.19, 0.178 g, 0.553 mmol, 92%) and **4b** (R_f = 0.25, 0.015 g, 0.047 mmol, 7%). ^{1}H NMR($CDCl_3$): 5.99 (dt, J = 39.2, 7.6 Hz,1H), 4.98 (m, 1H), 4.17-4.08 (m, 5H), 3.63 (dd, J = 7.6, 6.4 Hz, 1H), 1.56 (m, 10H), 1.32 (m, 6H). ^{13}C NMR($CDCl_3$): 151.85 (dd, J = 278.0, 233.2 Hz), 124.36 (dd, J = 27.6, 3.0 Hz), 110.6 (s), 68.67 (dd, J = 12.3, 6.9 Hz), 68.45 (m), 63.29 (dd, J = 5.3, 3.0 Hz), 36.09 (s), 35.17 (s), 24.97 (s), 23.78 (s), 16.17 (d, J = 6.1 Hz). ^{19}F NMR($CDCl_3$): -127.04 (dd, J = 99.0, 39.1 Hz, 1F). ^{31}P NMR($CDCl_3$): 4.68 (d, J = 98.9 Hz). MS (CI) m/z 323 (M^++1, 69.89), 99 ($OC_6H_{11}^+$, 100.00). HRMS, M^+, Found: 322.1354. Calcd for $C_{14}H_{24}FO_5P$, 322.1345. $[\alpha]^{20}_D$ = +51.68 (c = 0.15, EtOH).

(*Z*)-(3*R*)-Diethyl 1-Fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-enylphosphonate 4b. ^{1}H NMR ($CDCl_3$): 6.08 (ddd, J = 30.8, 26.8, 9.6 Hz, 1H), 5.41 (m, 1H), 4.16 (m, 5H), 3.62 (dd, J = 8.0, 6.0 Hz, 1H), 1.59 (m, 8H), 1.34 (m, 8H). ^{19}F NMR ($CDCl_3$): -118.34 (dd, J = 101.6, 26.3 Hz, 1F). ^{31}P NMR ($CDCl_3$): 3.74 (d, J = 101.0 Hz).

(3*R*)-Diethyl 1-Fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-phosphonate 5. A solution of **4** (0.128 g, 0.398 mmol) in absolute ethanol (8 mL) containing 10% Pd-C catalyst (10 mg) was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration and evaporation under reduced pressure gave compound **5** as a colourless liquid (0.126 g, 0.390 mmol, 98% yield). ^{1}H NMR ($CDCl_3$): 4.99-4.76 (m, 1H), 4.33-4.01 (m, 5H), 3.63-3.54 (m, 1H), 2.25-1.98 (m, 2H), 1.56 (m, 8H), 1.31 (m, 8H). ^{13}C NMR ($CDCl_3$): 109.70 (s), 109.66 (s), 86.14 (dd, J = 179.4, 171.8 Hz), 86.00 (dd, J = 179.4, 171.8 Hz), 71.92 (dd, J = 11.5, 3.0 Hz),

71.27 (dd, J = 11.5, 3.0 Hz), 68.94 (s), 68.33 (s), 63.09 (dd, J = 39.9, 6.9 Hz), 62.98 (dd, J = 33.7, 4.6 Hz), 36.70 (s), 36.1417 (s), 35.06 (s), 34.81 (s), 33.99 (d, J = 19.1 Hz), 16.40 (d, J = 6.1 Hz). ^{19}F NMR ($CDCl_3$): -207.52 (m), -212.53 (m). ^{31}P NMR ($CDCl_3$): 18.76 (d, J = 73.8 Hz), 18.47 (d, J = 73.8 Hz). MS (CI) m/z 325 (M^++1, 100.00). HRMS, M^+, Found: 324.1519. Calcd for $C_{14}H_{26}FO_5P$, 324.1502. $[\alpha]^{20}_D$ = -5.59 (c = 0.34, EtOH).

(3*R*)-Diethyl 1-Fluoro-3,4-dihydroxybut-1-phosphonate 6. TosOH (7 mg, 0.035 mmol, 0.10 eq.) was added to a solution of **5** (0.114 g, 0.352 mmol) in MeOH (5 mL), and the solution was stirred at room temperature for 24 h. After addition of solid $NaHCO_3$ to neutralize the reaction mixture, the solvent was removed under reduced pressure. Chromatograph got pure product (75 mg, 0.306 mmol, 87%). ^{1}H NMR ($CDCl_3$): 5.11-4.87 (m, 1H), 4.19-4.08 (m, 5H), 3.96 (br, 1H), 3.79 (br, 1H), 3.59 (m, 1H), 3.40 (m, 1H), 2.15-1.77 (m, 2H), 1.30 (t, J = 6.8 Hz, 8H). ^{19}F NMR ($CDCl_3$): -207.43 (m), -211.70 (m). ^{31}P NMR ($CDCl_3$): 19.89 (d, J = 74.0 Hz), 19.36 (d, J = 75.9 Hz). $[\alpha]^{20}_D$ = -13.42 (c = 0.73, EtOH).

Diethyl [1-fluoro-3 (S)-hydroxyl-4-(oleoyloxy)butyl]Phosphonate 7a. To the alcohol solution **6** and (42 mg, 47 μL, 0.147 mmol) of oleic acid in dry CH_2Cl_2 (1 mL) at rt was added dropwise a solution of DCC (30 mg, 0.147 mmol) and DMAP (6 mg, 0.048 mmol) in dry CH_2Cl_2 (1 mL). The solution was stirred at rt for 18 h and filtered, the solvent removed, and the residue was purified by chromatography (n-hexane/ethyl acetate 1:1, R_f= 0.28) to afford a waxy solid 12 mg. (0.026 mmol, 45%). ^{1}H NMR($CDCl_3$): 5.29 (m, 2H), 5.10-4.89 (m, 1H), 4.22-3.98 (m, 7H), 3.48 (br, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.18-2.03 (m, 2H), 1.93 (m, 4H), 1.58 (m, 2H), 1.33-1.22 (m, 28H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.84 (s), 173.81 (s), 129.92 (s), 129.64 (s), 86.49 (dd, J = 171.0, 172.6 Hz), 84.71 (dd, J = 171.1, 172.6 Hz), 68.06 (s), 67.48 (s), 66.01 (dd, J = 10.0, 3.8 Hz), 65.07 (dd, J = 13.1, 3.0 Hz), 63.55 (d, J = 6.9 Hz), 63.30 (d, J = 6.9 Hz), 63.06 (d, J = 6.9 Hz), 62.98 (d, J = 8.4 Hz), 34.36 (d, J = 19.9 Hz), 33.81 (d, J = 18.4 Hz), 31.82 (s), 29.67 (s), 29.61 (s), 29.43 (s), 29.23 (s), 29.09 (s), 27.13 (s), 27.08 (s), 24.86 (s), 22.59 (s), 16.35 (m), 14.02 (s). ^{19}F NMR

($CDCl_3$): -208.26 (1F, m), -211.75 (1F, m). ^{31}P NMR ($CDCl_3$): 19.36 (d, J = 73.8 Hz), 19.10 (d, J = 76.1 Hz). MS (CI) m/z 509.4 (M^++1, 29.75), 463.3 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 509.3400. Calcd for $C_{26}H_{51}FO_6P$, 509.3407. $[\alpha]^{20}_D$ = -2.61 (c = 2.38, MeOH).

Diethyl [1-fluoro-3 (S)-hydroxyl-4-(linoleoyloxy)butyl]Phosphonate 7b. Yield 61%. ^1H NMR ($CDCl_3$): 5.30 (m, 4H), 5.10-4.90 (m, 1H), 4.17-4.01 (m, 7H), 3.51 (br, 0.5H), 3.24 (br, 0.5H), 2.70 (m, 2H), 2.29 (t, J = 6.8 Hz, 3H), 2.15-1.98 (m, 6H), 1.57 (m, 2H), 1.29 (m, 20H), 0.83 (t, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.77 (s), 130.10 (s), 129.91 (s), 127.95 (s), 127.80 (s), 85.95 (dd, J = 178.7, 171.1 Hz), 85.19 (dd, J = 179.5, 171.3 Hz), 68.02 (s), 67.45 (s), 65.99 (dd, J = 9.3, 3.9 Hz), 65.00 (dd, J = 9.8, 9.7 Hz), 63.40 (dd, J = 25.5, 6.8 Hz), 63.00 (dd, J = 6.8, 6.8 Hz), 34.14 (dd, J = 41.4, 19.2 Hz), 31.41 (s), 29.49 (s), 29.24 (s), 29.07(s), 29.00 (s), 27.09 (s), 25.52 (s), 24.78 (s), 22.46 (s), 16.36 (d, J = 4.5 Hz), 13.96 (s). ^{19}F NMR ($CDCl_3$): -208.25 (m), -211.79 (m). ^{31}P NMR ($CDCl_3$): 19.37 (d, J = 73.8 Hz), 19.09 (d, J = 76.1 Hz). MS (CI) m/z 507 (M^++1, 100.00), 463.3 (M^+-OC_2H_5, 48.19). HRMS, M^+, Found: 506.3174. Calcd for $C_{26}H_{48}FO_6P$, 506.3173. $[\alpha]^{20}_D$ = -4.29 (c = 0.14, EtOH).

Diethyl [1-fluoro-3 (S)-hydroxyl-4-(palmitoyloxy)butyl]Phosphonate 7c. 51% yield. ^1H NMR($CDCl_3$): 5.11-4.90 (m, 1H), 4.23-3.99 (m, 7H), 3.42 (br, 1H), 2.31 (t, J = 7.6 Hz, 2H), 2.19-1.90 (m, 2H), 1.68-1.55 (m, 2H), 1.33 (t, J = 6.8 Hz, 6H), 1.60 (m, 24H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR($CDCl_3$): 173.92 (s), 173.89 (s), 86.56 (dd, J = 171.0, 168.2 Hz), 84.78 (dd, J = 171.0, 168.2 Hz), 68.10 (s), 67.53 (s), 66.11 (dd, J = 9.3, 3.8 Hz), 65.21 (dd, J = 13.0, 3.1 Hz), 63.48 (dd, J = 24.6, 6.9 Hz), 63.05 (dd, J = 9.3, 6.8 Hz), 49.03 (s), 34.36 (d, J = 19.9 Hz), 31.87 (s), 29.63 (s), 29.60 (s), 29.41 (s), 29.22 (s), 29.09 (s), 25.59 (s), 24.86 (s), 22.63 (s), 16.41 (d, J = 5.3 Hz), 16.37 (d, J = 4.6 Hz), 14.06 (s). ^{19}F NMR($CDCl_3$): -208.37 (1F, m), -211.62 (1F, m). ^{31}P NMR($CDCl_3$): 19.34 (d, J = 73.8 Hz), 19.11 (d, J = 76.1 Hz). MS (CI) m/z 483.4 (M^++1, 55.29), 437.4 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 483.3244. Calcd for $C_{24}H_{49}FO_6P$, 483.3251. $[\alpha]^{20}_D$ = -2.20 (c = 1.00, MeOH).

[1-Fluoro-3 (S)-hydroxyl-4-(oleoyloxy)butyl]phosphonate 8a. Thoroughly dried

(64 mg, 0.126 mmol, 5 h under high vacuum) was dissolved in anhydrous methylene chloride (1 mL) at room temperature. Bromotrimethylsilane (193 mg, 1.260 mmol) was added with a dry syringe and stirred 4 h. TLC indicated that all of the reactant had disappeared, then the solvent removed under reduced pressure and dried under vacuum. The residue was dissolved in 95% methanol (1 mL) for 1h, then the solvent removed under reduced pressure and dried under vacuum, got final product 55 mg. (0.121 mmol, 96% yield.). ^{1}H NMR (CD_3OD): 5.34 (m, 2H), 5.21-5.17 (m, 1H), 4.79 (m, 1H), 3,68 (dd, J = 11.60, 4.40 Hz, 1H), 3.57 (m, 1H), 2.35 (m, 4H), 2.01 (m, 4H), 1.63 (m, 2H), 1.33-1.22 (m, 20H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CD_3OD): 174.33 (s), 174.17 (s), 130.84 (s), 130.74 (s), 88.16 (dd, J = 170.3, 168.7 Hz), 86.39 (dd, J = 170.3, 168.7 Hz), 71.30 (dd, J = 14.6, 2.3 Hz), 69.52 (dd, J = 14.6, 2.3 Hz), 35.12 (d, J = 19.3 Hz), 34.93 (d, J = 18.9 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). ^{19}F NMR (CD_3OD): -208.60 (1F, m), -210.99 (1F, m). ^{31}P NMR (CD_3OD): 16.21 (d, J = 72.7 Hz), 15.95 (d, J = 73.8 Hz). MS (CI) m/z 435.3 (M^+-OH, 60.85), 283.3 (M^+-C_4H_9-CFH_3PO_3, 100.00). HRMS, M^+-OH, Found: 435.2678. Calcd for $C_{22}H_{41}FO_5P$, 435.2676. $[\alpha]^{20}_D$ = -2.13 (c = 0.14, MeOH).

[1-Fluoro-3 (S)-hydroxyl-4-(linoleoyloxy)butyl]phosphonate 8b. 93% yield. ^{1}H NMR (CD_3OD): 5.30 (m, 4H), 5.10-4.90 (m, 1H), 4.17-4.01 (m, 3H), 3.51 (br, 0.5H), 3.24 (br, 0.5H), 2.70 (m, 2H), 2.29 (t, J = 6.8 Hz, 3H), 2.15-1.98 (m, 6H), 1.57 (m, 2H), 1.29 (m, 14H), 0.83 (t, J = 6.4 Hz, 3H). ^{13}C NMR??? (CD_3OD): 174.33 (s), 174.17 (s), 130.84 (s), 130.74 (s), 88.16 (dd, J = 170.3, 168.7 Hz), 86.39 (dd, J = 170.3, 168.7 Hz), 71.30 (dd, J = 14.6, 2.3 Hz), 69.52 (dd, J = 14.6, 2.3 Hz), 35.12 (d, J = 19.3 Hz), 34.93 (d, J = 18.9 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). ^{19}F NMR (CD_3OD): -208.25 (m), -211.79 (m). ^{31}P NMR (CD_3OD): 19.37 (d, J = 73.8 Hz), 19.09 (d, J = 76.1 Hz). HRMS, M^+-OH, Found: 433.2502. Calcd for $C_{22}H_{39}FO_5P$, 433.2519. $[\alpha]^{20}_D$ = -2.78 (c = 0.22, MeOH).

[1-Fluoro-3 (S)-hydroxyl-4-(palmitoyloxy)butyl]Phosphonate 8c. 91% yield. ^{1}H

NMR(CD_3OD): 5.27-5.18 (m, 1H), 4.78 (m, 1H), 3,68 (dd, J = 10.80, 4.00 Hz, 1H), 3.57 (m, 1H), 2.40-2.25 (m, 4H), 1.64 (m, 2H), 1.33-1.22 (m, 24H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR($CDCl_3$): 172.33 (s), 172.30 (s), 87.06 (dd, J = 170.3, 168.7 Hz), 85.29 (dd, J = 170.3, 168.7 Hz), 69.33 (dd, J = 14.2, 2.4 Hz), 67.56 (dd, J = 14.2, 2.4 Hz), 33.04 (d, J = 7.7 Hz), 31.92 (s), 31.06 (s), 28.77 (s), 28.75 (s), 28.71 (s), 28.58 (s), 28.47 (s), 28.39 (s), 28.15 (s), 24.05 (s), 23.97 (s), 23.92 (s), 21.72 (s), 12.48 (s). ^{19}F NMR($CDCl_3$): -208.73 (1F, m), -211.07 (1F, m). ^{31}P NMR($CDCl_3$): 16.21 (d, J = 72.7 Hz), 15.95 (d, J = 73.8 Hz). MS (CI) m/z 409.2 (M^++1-OH-CH_3, 2.29), 225.2 (M^+-$C_{14}H_{29}$-OH, 100.00). HRMS, M^+-OH-CH_3, Found: 408.2432. Calcd for $C_{20}H_{38}FO_5P$, 408.2441. $[\alpha]^{20}_D$ = -1.83 (c = 0.17, MeOH).

Diethyl [1-fluoro-3 (S)-hydroxyl-4-*(tetra*-butyldimethylsilyl)-butyl]Phosphonate 9. To a solution of phosphate **6** (0.386 g, 1.582 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (0.250 g, 1.661 mmol, 1.05 eq.) in anhydrous CH_2Cl_2 (8 mL) was added 4- dimethylaminopyridine(DMAP) (0.010 g, 0.080 mmol, 0.05 eq.) and triethylamine (0.168 g, 1.661 mmol, 1.05 eq.). The reaction mixture was stirred at room temperature for 16 h. The solution was diluted with CH_2Cl_2 (20 mL), and the solution was washed with saturated NH_4Cl aqueous solution and brine. After drying with anhydrous Na_2SO_4, the organic layer was concentrated in vacuo. The residue was purified by chromatography (Ethyl acetate/hexane = 1:1, R_f = 0.13) to afford a colorless liquid (0.413 g, 1.155 mmol, 73%). ^1H NMR ($CDCl_3$): 5.12-4.88 (m, 1H), 4.19 (m, 4H), 3.96-3.82 (m, 1H), 3.67-3.43 (m, 2H), 2.83 (d, J = 4.4 Hz, 0.5H), 2.60 (d, J = 5.2 Hz, 0.5H), 2.23-1.79 (m, 2H), 1.33 (t, J = 6.8 Hz, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$): 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 68.47 (dd, J = 10.0, 3.8 Hz), 67.10 (dd, J = 13.0, 3.8 Hz), 66.96 (s), 66.39 (s), 63.26 (dd, J = 15.3, 6.8 Hz), 62.86 (dd, J = 9.3, 6.9 Hz), 33.81 (d, J = 18.4 Hz), 25.81 (s), 18.24 (s), 18.22 (s), 23.78 (s), 16.49 (d, J = 3.8 Hz), 16.38 (d, J = 3.8 Hz), -5.43 (s), -5.47 (s). ^{19}F NMR ($CDCl_3$): -207.18 (m), -211.77 (m). ^{31}P NMR ($CDCl_3$): 19.60 (d, J = 75.0 Hz), 19.24 (d, J = 77.1 Hz). MS (CI) m/z 359.0 (M^++1, 100.00). HRMS, M^++1, Found: 359.1819. Calcd for $C_{14}H_{33}FO_5PSi$, 359.1819. $[\alpha]^{20}_D$ = -20.91

(c = 0.88, EtOH).

Diethyl [1-fluoro-3 (S)-*O*-methyl-4-*(tetra*-butyldimethylsilyl)-butyl]Phosphonate 10.

Method A: To a vigorously stirred mixture of **9** (0.046 g, 0.136 mmol) and FBA (42% aqueous fluoroboric acid, 0.028 g, 20 μL) in CH_2Cl_2 (1 mL) was added $TMSCHN_2$ (2.0M hexane solution, 136 μL) at 0°C. The stirring was continued at 0°C, and three further portions of $TMSCHN_2$ (68 μL × 3) were added dropwise at intervals of 20 min. The mixture was stirred at 0°C for further 30 min and at rt for another 30 min, added 10% $NaHCO_3$ solution (0.1 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (Ethyl acetate/hexane = 2:3, R_f= 0.31) to afford a colorless liquid (0.034 g, 0.091 mmol, 67%).

Method B: To a stirred mixture of **9** (0.022 g, 0.061 mmol) and proton sponge (1,8-bis(dimethylamino)naphthalene) (0.016 g, 0.073 mmol) in CH_2Cl_2 (1 mL) was added Meerwein's trimethyloxonium tetrafluoroborate (0.009 g, 0.061 mmol) at room temperature. The resulting solution was stirred at room temperature for 14 days before it was diluted with CH_2Cl_2 (2 mL) and quenched with water (0.1mL). The solution was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (Ethyl acetate/hexane = 2:3, R_f= 0.31) to afford a colorless liquid (0.010 g, 0.027 mmol, 43%).

^1H NMR ($CDCl_3$): 5.04-4.89 (m, 1H), 4.19 (m, 4H), 3.70-3.58 (m, 2H), 3.46 (m, 1H), 3.42 (s, 1.5H), 3.37 (s, 1.5H), 2.14-1.79 (m, 2H), 1.31 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$): 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 64.68 (s), 64.40 (s), 63.08 (m), 62.75 (m), 58.46 (s), 57.59 (s), 32.67 (d, J = 22.2 Hz), 31.77 (d, J = 19.2 Hz), 25.84 (s), 18.25 (s), 18.22 (s), 16.42 (d, J = 6.1 Hz), -5.46 (s). ^{19}F NMR ($CDCl_3$): -207.71 (m), -212.49 (m). ^{31}P NMR ($CDCl_3$): 19.76 (d, J = 76.1 Hz), 19.23 (d, J = 76.1Hz). MS (CI) m/z 373.19 (M^++1, 100.00). HRMS, M^++1, Found: 373.1974. Calcd for $C_{15}H_{34}FO_5PSi$, 373.1975. $[\alpha]^{20}_D$ = -13.96 (c = 0.48, EtOH).

Diethyl [1-fluoro-3 (S)-hydroxyl-4-*O*-methyl-butyl]Phosphonate 11. To a stirred mixture of **9** (0.022 g, 0.061 mmol) and proton sponge (1,8-bis(dimethylamino)naphthalene) (0.016 g, 0.073 mmol) in CH_2Cl_2 (1 mL) was added Meerwein's trimethyloxonium tetrafluoroborate (0.009 g, 0.061 mmol) at room temperature. The resulting solution was stirred at room temperature for 4 days before it was diluted with CH_2Cl_2 (2 mL) and quenched with water (0.1mL). After evaporated the solution, ethyl acetate was added and the solution was washed with saturated NH4Cl.The solution was dried with anhydrous and concentrated. The residue was purified by chromatography (CH2Cl2/CH3OH = 2:3, R_f= 0.31) to afford a colorless liquid (0.010 g, 0.027 mmol, 43%). ^{1}H NMR ($CDCl_3$): 5.10-4.89 (m, 1H), 4.13 (m, 4H), 4.10-3.90 (m, 1H), 3.41-3.40 (m, 3H), 3.33 (s, 3H), 2.15-2.01 (m, 2H), 1.30 (m, 6H). ^{19}F NMR ($CDCl_3$): -207.59 (m), -212.02 (m). ^{31}P NMR ($CDCl_3$): 19.76 (d, J = 76.1 Hz), 19.23 (d, J = 76.1Hz).

Diethyl [1-fluoro-3 (S) -(oleoyloxy)-4-*O*-methyl-butyl]Phosphonate 12a. To a solution of alcohol **11** (0.036 g, 0.140 mmol) and oleic acid (0.043 g, 0.154 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DCC (0.040 g, 0.196 mmol) and DMAP (0.010 g, 0.084 mmol) in dry CH_2Cl_2 (4 mL) at 0°C. The solution was stirred for 16 h at rt, filtered, concentrated *in vacuo*, and the residue was purified on silica gel (n-hexane/ethyl acetate, HE: AE = 1:1, R_f= 0.34) to afford ester. (0.061 g, 0.117 mmol, 83%) as a waxy solid. ^{1}H NMR ($CDCl_3$): 5.31 (m, 2H), 5.21-5.16 (m, 1H), 4.93-4.77 (m, 1H), 4.19 (m, 4H), 3.49 (m, 1H), 3.43 (m, 1H), 3.32 (s, 3H), 2.32-2.13 (m, 4H), 1.98 (m, 4H), 1.59 (m, 2H), 1.34-1.23 (m, 26H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.20 (s), 173.07 (s), 129.95 (s), 129.69 (s), 84.85 (dd, J = 178.7, 171.0 Hz), 84.05 (dd, J = 178.7, 171.0 Hz), 73.46 (s), 73.03 (s), 69.35 (d, J = 14.6 Hz), 67.95 (d, J = 15.4 Hz), 63.32 (d, J = 6.8 Hz), 62.97 (d, J = 6.2 Hz), 59.16 (d, J = 4.6 Hz), 34.33 (s), 34.28 (s), 31.85 (s), 31.76 (s), 29.71 (s), 29.65 (s), 29.47 (s), 29.27 (s), 29.13 (s), 29.07 (s), 29.02 (s), 27.16 (s), 27.13 (s), 24.92 (s), 24.83 (s), 16.41 (m), 14.05 (s). ^{19}F NMR ($CDCl_3$): -208.71 (m), -211.47 (m). ^{31}P NMR ($CDCl_3$): 18.57 (d, J = 73.8 Hz), 18.21 (d, J = 76.1 Hz). MS (CI) m/z 523.4 (M^++1, 100.00). HRMS,

M^++1, Found: 523.3586. Calcd for $C_{27}H_{53}FO_6P$, 523.3564.

Diethyl [1-fluoro-3 (S) -(palmitoyloxy)-4-*O*-methyl-butyl]Phosphonate 12b. Same procedure as **12a**, 87%. ^1H NMR ($CDCl_3$): 5.21 (m, 1H), 4.99-4.65 (m, 1H), 4.15 (m, 4H), 3.54 (m, 1H), 3.42 (m, 1H), 3.28 (s, 3H), 2.31-2.09 (m, 4H), 1.57 (m, 2H), 1.31 (m, 4H), 1.17 (m, 26H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.14 (s), 173.05 (s), 84.81 (dd, J = 178.7, 171.0 Hz), 84.00 (dd, J = 178.7, 171.0 Hz), 73.41 (s), 72.98 (s), 69.31 (d, J = 14.6 Hz), 67.90 (d, J = 15.4 Hz), 63.27 (d, J = 6.8 Hz), 62.91 (d, J = 6.2 Hz), 59.11 (d, J = 4.6 Hz), 34.13 (s), 34.12 (s), 32.95 (s), 29.63 (s), 29.60 (s), 29.41 (s), 29.30 (s), 29.21 (s), 29.08 (s), 24.87 (s), 22.61 (s), 16.40 (d, J = 5.3 Hz), 14.06 (s). ^{19}F NMR ($CDCl_3$): -208.65 (m), -211.49 (m). ^{31}P NMR ($CDCl_3$): 18.51 (d, J = 73.7 Hz), 18.15 (d, J = 75.4 Hz). MS (CI) m/z 497.4 (M^++1, 100.00). HRMS, M^++1, Found: 497.3398. Calcd for $C_{25}H_{51}FO_6P$, 497.3407.

[1-Fluoro-3(S)-(oleoyloxy)-4-*O*-methyl-butyl]Phosphonate 13a. 93% yield. ^1H NMR (CD_3OD): 5.34 (m, 2H), 5.26-5.22 (m, 1H), 4.91-4.4.40 (m, 1H), 3.57 (m, 1H), 3.47 (m, 1 H), 3.36 (s, 3H), 2.37-2.13 (m, 4H), 2.02 (m, 4H), 1.61 (m, 2H), 1.32-1.29 (m, 22H), 0.89 (t, J = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): 172.89 (s), 172.72 (s), 128.90 (s), 128.87 (s), 86.33 (dd, J = 178.7, 171.0 Hz), 85.52 (dd, J = 178.7, 171.0 Hz), 72.76 (s), 72.24 (s), 69.25 (s), 69.11 (s), 57.36 (s), 33.20 (s), 33.13 (s), 31.06 (s), 30.95 (s), 28.84 (s), 28.80 (s), 28.61 (s), 28.45 (s), 28.35 (s), 28.29 (s), 28.18 (s), 28.11 (s), 26.13 (s), 24.09 (s), 21.74 (s), 12.46 (s). ^{19}F NMR (CD_3OD): -208.66 (m), -211.40 (m). ^{31}P NMR (CD_3OD): 16.64 (s), 16.22 (s). MS (CI) m/z 449.2 (M^++1-H_2O, 100.00). HRMS, M^++1, Found: 449.2824. Calcd for $C_{23}H_{43}FO_5P$, 449.2832.

[1-Fluoro-3(S)-(palmitoyloxy)-4-*O*-methyl-butyl]Phosphonate 13b. 95% yield. ^1H NMR (CD_3OD): 5.22 (m, 1H), 4.98-4.66 (m, 1H), 3.61 (m, 1H), 3.48 (m, 1H), 3.37 (s, 3H), 2.34 (t, J = 6.0 Hz, 2H), 2.13-1.99 (m, 2H), 1.61 (m, 2H), 1.34 (m, 26H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (CD_3OD): 175.15 (s), 86.40 (dd, J = 178.7, 171.0 Hz), 85.59 (dd, J = 178.7, 171.0 Hz), 77.14 (s), 75.72 (s), 65.83 (s), 65.64 (s), 58.34 (s), 57.70 (s), 33.02 (d, J = 7.7 Hz), 31.90 (s), 31.03 (s), 28.76 (s), 28.78 (s), 28.73 (s), 28.56 (s), 28.45 (s), 28.36 (s), 28.14 (s), 24.02 (s), 23.96 (s), 23.90 (s), 21.70 (s),

12.47 (s). ^{19}F NMR (CD_3OD): -207.41 (m), -212.34 (m). ^{31}P NMR (CD_3OD): 17.34 (d, J = 73.7 Hz), 17.26 (d, J = 76.1 Hz). MS (CI) m/z 423.2 (M^+-OH, 79.26), 185.0 (M^+-$C_{15}H_{31}CO_2H$, 100.00). HRMS, M^++1, Found: 423.2671. Calcd for $C_{21}H_{41}FO_5P$, 423.2676.

Diethyl [1-fluoro-3 (S)-*O*-methyl-4-hydroxyl-butyl]Phosphonate 14. A solution of **10** (0.024 g, 0.063 mmol) in THF (1 mL) was treated successively with acetic acid (15 μL, 0.254 mmol) and tetrabutylammoniumfluoride trihydrate (0.080 g, 0.254 mmol) at room temperature. After stirring for 16 h, the reaction was completed (TLC control), then the solvent was evaporated under reduced pressure and the crude product was purified by pass through a short column (CH_2Cl_2 /CH_3OH = 30 :1 , R_f= 0.13) to afford a colorless liquid (0.015 g, 0.059 mmol, 93%). ^1H NMR ($CDCl_3$): 5.02-4.79 (m, 1H), 4.18 (m, 4H), 3.83-3.67 (m, 1H), 3.59-3.46 (m, 2H), 3.42 (s, 1.5H), 3.38 (s, 1.5H), 2.21-1.98 (m, 3H), 1.35 (m, 6H). ^{13}C NMR ($CDCl_3$): 85.66 (dd, J = 184.8, 177.9 Hz), 63.32 (s), 63.15 (s), 62.92 (m), 57.90 (s), 57.14 (s), 32.29 (d, J = 19.9 Hz), 30.64 (d, J = 18.4 Hz), 16.43 (m). ^{19}F NMR ($CDCl_3$): -207.03 (m), -211.39 (m). ^{31}P NMR ($CDCl_3$): 19.40 (d, J = 75.0 Hz), 18.89 (d, J = 75.0 Hz).

Diethyl [1-fluoro-3 (S)-*O*-methyl-4-(oleoyloxy)-butyl]Phosphonate 15a.

Method A: To a vigorously stirred mixture of **7a** (0.030 mg, 0.059 mmol) and FBA (42% aqueous fluoroboric acid, 0.012 g, 9 μL) in CH_2Cl_2 (1 mL) was added $TMSCHN_2$ (2.0M hexane solution, 59 μL) at 0°C. The stirring was continued at 0°C, and three further portions of $TMSCHN_2$ (30 μL × 3) were added dropwise at intervals of 20 min. The mixture was stirred at 0°C for further 30 min and at rt for another 30 min, added 10% $NaHCO_3$ solution (0.1 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (Ethyl acetate/hexane = 1:2, R_f= 0.11) to afford a colorless liquid (0.026 g, 0.051 mmol, 86%).

Method B: To a solution of diol (0.016 g, 0.063 mmol) and oleic acid (0.020 g, 0.069 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of DCC (0.016 g, 0.076 mmol) and DMAP (0.005 g, 0.038 mmol) in dry CH_2Cl_2 (1 mL) at 0°C. The solution was stirred

for 16 h at rt, filtered, concentrated *in vacuo*, and the residue was purified on silica gel (n-hexane/ethyl acetate, HE: AE = 2:1, R_f= 0.11) to afford ester. (0.030 g, 0.057 mmol, 91%) as a waxy solid.

^{1}H NMR ($CDCl_3$): 5.31 (m, 4H), 5.03-4.84 (m, 1H), 4.26-4.13 (m, 4H), 4.11-4.00 (m, 1.5H), 3.81 (m, 0.5H), 3.42 (s, 1.5H), 3.38 (s, 1.5H), 2.32 (t, J = 6.0 Hz, 2H), 2.21-2.04 (m, 2H), 2.01 (m, 4H), 1.61 (m, 2H), 1.56-1.24 (m, 26H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.60 (s), 129.98 (s), 129.70 (s), 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 75.47 (d, J = 8.4 Hz), 74.90 (d, J = 12.6 Hz), 64.56 (d, J = 3.6 Hz), 64.45 (d, J = 5.4 Hz), 63.26 (dd, J = 10.0, 5.6 Hz), 62.88 (t, J = 6.9 Hz), 58.21 (s), 57.50 (s), 34.15 (s), 33.81 (d, J = 18.4 Hz), 31.88 (s), 29.74 (s), 29.67 (s), 29.49 (s), 29.29 (s), 29.15 (s), 29.08 (s), 27.19 (s), 27.14 (s), 24.88 (s), 22.66 (s), 16.43 (m), 14.08 (s). ^{19}F NMR ($CDCl_3$): -207.30 (m), -212.72 (m). ^{31}P NMR ($CDCl_3$): 19.25 (d, J = 76.1 Hz), 18.71 (d, J = 75.0 Hz). MS (CI) m/z 523.3 (M^++1, 100.00). HRMS, M^++1, Found: 523.3568. Calcd for $C_{27}H_{53}FO_6P$, 523.3564. $[\alpha]^{20}_D$ = -3.08 (c = 0.26, EtOH).

Diethyl [1-fluoro-3 (S)-*O*-methyl-4-(linolenoyloxy)-butyl]Phosphonate 15b.

Method B: ^{1}H NMR ($CDCl_3$): 5.32 (m, 6H), 5.02-4.82 (m, 1H), 4.25-4.13 (m, 4H), 4.08 (dd, J = 12.0, 4.4 Hz, 1H), 4.01 (dd, J = 12.0, 4.8 Hz, 1H), 3.65-3.55 (m, 1H), 3.41 (s, 1.5H), 3.37 (s, 1.5H), 2.76 (t, J = 8.0 Hz, 4H), 2.29 (t, J = 8.0 Hz, 2H), 2.19-1.92 (m, 6H), 1.58 (m, 2H), 1.34-1.21 (m, 14H), 0.93 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.50 (s), 131.88 (s), 130.18 (s), 128.22 (s), 128.18 (s), 127.67 (s), 127.05 (s), 85.47 (dd, J = 179.4, 171.8 Hz), 85.25 (dd, J = 179.4, 171.8 Hz), 75.41 (d, J = 12.3 Hz), 73.92 (d, J = 11.5 Hz), 64.56 (s), 64.46 (s), 63.23 (dd, J = 10.0, 6.9 Hz), 62.84 (t, J = 6.9 Hz), 58.16 (s), 57.45 (s), 34.09 (s), 34.15 (s), 32.94 (d, J = 21.1 Hz), 31.67 (d, J = 21.1 Hz), 29.51 (s), 29.10 (s), 29.02 (s), 27.13 (s), 25.55 (s), 25.46 (s), 24.83 (s), 20.48 (s), 16.40 (m), 14.20 (s). ^{19}F NMR ($CDCl_3$): -207.38 (m), -212.72 (m). ^{31}P NMR ($CDCl_3$): 19.25 (d, J = 75.0 Hz), 18.70 (d, J = 75.0 Hz). MS (CI) m/z 519.4 (M^++1, 84.26), 225.2 (M^+-$C_{17}H_{29}CO_2H$-CH_3, 100.00). HRMS, M^++1, Found: 519.3254. Calcd for $C_{27}H_{49}FO_6P$, 519.3251.

Diethyl [1-fluoro-3 (S)-*O*-methyl-4-(palmitoyloxy)-butyl]Phosphonate 15c. **Method A**: 88% yield. **Method B**: 83% yield. ^{1}H NMR ($CDCl_3$): 5.04-4.76 (m, 1H), 4.26-4.14 (m, 4H), 4.11-4.00 (m, 1.5H), 3.81 (m, 0.5H), 3.42 (s, 1.5H), 3.38 (s, 1.5H), 2.30 (t, J = 8.0 Hz, 2H), 2.20-2.01 (m, 2H), 1.60 (m, 2H), 1.34 (t, J = 8.0 Hz, 6H), 1.31 (m, 26H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): 173.61 (s), 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 75.47 (d, J = 9.3 Hz), 74.90 (d, J = 16.1 Hz), 64.59 (s), 64.50 (s), 63.32 (dd, J = 10.0, 6.8 Hz), 62.88 (t, J = 6.9 Hz), 58.20 (s), 57.50 (s), 34.17 (s), 34.15 (s), 32.97 (d, J = 21.5 Hz), 31.90 (s), 29.66 (s), 29.62 (s), 29.44 (s), 29.33 (s), 29.24 (s), 29.11 (s), 24.89 (s), 22.64 (s), 16.43 (d, J = 5.3 Hz), 14.09 (s). ^{19}F NMR ($CDCl_3$): -207.39 (m), -212.73 (m). ^{31}P NMR ($CDCl_3$): 19.26 (d, J = 75.0 Hz), 18.71 (d, J = 75.0 Hz). MS (CI) m/z 497.4 (M^++1, 100.00). HRMS, M^++1, Found: 497.3402. Calcd for $C_{25}H_{51}FO_6P$, 497.3407. $[\alpha]^{20}_D$ = -3.33 (c = 0.36, EtOH).

[1-Fluoro-3 (S)-*O*-methyl-4-(oleoyloxy)-butyl]Phosphonate 16a. 95% yield. ^{1}H NMR (CD_3OD): 5.33 (m, 2H), 4.92-4.77 (m, 1H), 4.34-4.02 (m, 2H), 3.72-3.61 (m, 1H), 3.44 (m, 1.5H), 3.39 (s, 1.5H), 2.34 (m, 2H), 2.16-2.09 (m, 2H), 2.03 (m, 4H), 1.61 (m, 2H), 1.32-1.29 (m, 22H), 0.89 (t, J = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): 175.18 (s), 130.89 (s), 130.80 (s), 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 77.17 (d, J = 12.3 Hz), 75.78 (d, J = 12.6 Hz), 65.88 (s), 65.73 (s), 58.38 (s), 57.75 (s), 34.96 (s), 34.95 (s), 34.08 (d, J = 19.9 Hz), 33.06 (s), 32.82 (d, J = 20.0 Hz), 30.84 (s), 30.79 (s), 30.61 (s), 30.45 (s), 30.35 (s), 30.27 (s), 30.17 (s), 28.13 (s), 26.03 (s), 23.74 (s), 14.45 (s). ^{19}F NMR (CD_3OD): -207.35 (m), -212.19 (m). ^{31}P NMR (CD_3OD): 17.41 (d, J = 75.0 Hz), 16.87 (d, J = 75.0 Hz). MS (CI) m/z 449.2 (M^++1-H_2O, 100.00), 185.0 (M^+-$C_{17}H_{33}CO_2H$, 72.11). HRMS, M^++1, Found: 449.2823. Calcd for $C_{23}H_{43}FO_5P$, 449.2832. $[\alpha]^{20}_D$ = -0.94 (c = 0.32, MeOH).

[1-Fluoro-3 (S)-*O*-methyl-4-(linolenoyloxy)-butyl]Phosphonate 16b. ^{1}H NMR (CD_3OD): 5.40-5.26 (m, 6H), 4.94-4.76 (m, 1H), 4.27 (dd, J = 36.0, 8.0 Hz, 1H), 4.08 (dd, J = 32.0, 12.0 Hz, 1H), 3.65 (m, 1H), 3.44 (s, 1.5H), 3.39 (s, 1.5H), 2.80 (m, 4H), 2.13-1.99 (m, 2H), 2.14-1.99 (m, 6H), 1.61 (t, J = 8.0 Hz, 3H), 1.33 (m, 8H),

0.97 (t, J = 8.0 Hz, 3H). ^{13}C NMR (CD_3OD): 173.10 (s), 130.73 (s), 129.07 (s), 127.21 (s), 127.19 (s), 126.85 (s), 126.23 (s), 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 75.14 (d, J = 12.2 Hz), 73.73 (d, J = 14.6 Hz), 63.87 (s), 63.72 (s), 56.39 (s), 55.75 (s), 32.95 (s), 32.93 (s), 32.06 (d, J = 18.4 Hz), 30.80 (d, J = 19.9 Hz), 28.67 (s), 28.25 (s), 28.18 (s), 28.14 (s), 26.15 (s), 24.52 (s), 24.41 (s), 24.01 (s), 19.49 (s), 12.67 (s). ^{19}F NMR (CD_3OD): -207.34 (m), -212.21 (m). ^{31}P NMR (CD_3OD): 17.39 (d, J = 72.9 Hz), 17.03 (d, J = 73.8 Hz). MS (CI) m/z 445.2 (M^+-OH, 62.43), 185.0 (M^+-$C_{17}H_{29}CO_2H$, 100.00). HRMS, M^++1, Found: 445.2507. Calcd for $C_{23}H_{39}FO_5P$, 445.2519.

[1-Fluoro-3 (S)-*O*-methyl-4-(palmitoyloxy)-butyl]Phosphonate 16c. 97% yield. ^{1}H NMR (CD_3OD): 4.95-4.78 (m, 1H), 4.34-4.30 (m, 1H), 4.24-4.14 (m, 1H), 3.72-3.61 (m, 1H), 3.44 (s, 1.5H), 3.39 (s, 1.5H), 2.34 (t, J = 6.0 Hz, 2H), 2.13-1.99 (m, 2H), 1.60 (m, 2H), 1.33 (m, 26H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (CD_3OD): 175.20 (s), 86.43 (dd, J = 178.7, 171.0 Hz), 85.63 (dd, J = 178.7, 171.0 Hz), 77.17 (d, J = 8.5 Hz), 75.76 (d, J = 16.1 Hz), 65.85 (s), 65.69 (s), 58.37 (s), 57.74 (s), 34.98 (s), 34.56 (s), 34.08 (d, J = 22.12 Hz), 33.08 (s), 32.82 (d, J = 18.40 Hz), 30.78 (s), 30.77 (s), 30.71 (s), 30.60 (s), 30.48 (s), 30.40 (s), 30.18 (s), 26.04 (s), 23.74 (s), 12.48 (s). ^{19}F NMR (CD_3OD): -207.42 (m), -212.27 (m). ^{31}P NMR (CD_3OD): 17.36 (d, J = 73.8 Hz), 17.01 (d, J = 75.0 Hz). MS (CI) m/z 423.2 (M^+-OH, 85.63), 185.0 (M^+-$C_{15}H_{31}CO_2H$, 100.00). HRMS, M^++1, Found: 423.2673. Calcd for $C_{21}H_{41}FO_5P$, 423.2676. $[\alpha]^{20}_D$ = -2.27 (c = 0.22, MeOH).

V. Synthesis of Monofluorinated LPA Analogs

1-fluorodeoxy-(2*R*)-acyl-*sn*-glycerol-3-phosphates **1a** and **Ib** were synthesized from commercially available (*S*)-isopropylideneglycerol **5** (Figure 11). Alcohol **5** was first phosphorylated with dimethylphosphoryl chloride in the presence of *t*-BuOK to give dimethylphosphate **6** in 92% yield. Next, phosphate **6** was converted to 1-hydroxyl-2-(*S*)-(TBDMS)-3-phosphate in three steps. Acetonide hydrolysis with *p*TsOH/MeOH gave a crude diol, which was converted directly to the bis-silyl ether **8** by treatment with TBDMS-Cl and

imidazole in anhydrous DMF. The more labile primary TBDMS was then cleaved selectively using pyridium-HF in pyridine-THF at rt. Using an optimized selective deprotection, a 63% yield was obtained. Nucleophilic displacement of hydroxyl with DAST in anhydrous CH_2Cl_2 gave the corresponding monofluorinated compound **10**, without affecting the 2-position TBDMS ether. The stable TBDMS ether was further deprotected with *tetra*-(*n*-butyl)ammonium fluoride (TBAF) in THF to give the secondary alcohol; neutralization of TBAF with acetic acid permitted this desilylation to occur without phosphate migration. DCC-promoted esterification of **11** with either oleic acid or palmitic acid provided good yields of esters **12a** and **12b**. Finally, treatment of each ester **12** with bromotrimethylsilane and subsequent addition of 5% aq. methanol provided the desired fluorinated LPA analogues **1a** and **1b** in nearly quantitative yield. Using the same procedure, the (2*S*)-LPA analogue **1c** was obtained from (*R*)-isopropylideneglycerol **13** in the analogous eight steps (5.6% overall yield) (Figure 11).

The 1-acyl-(2*R*)-fluorinedeoxy-*sn*-glycerol-3-phosphates **2** were synthesized from (*R*)-isopropylideneglycerol **13** (Figure 12). As described above for diol **7**, diol **14** was prepared by phosphorylation with dimethylphosphoryl chloride followed by acid hydrolysis. The primary alcohol was selectively protected as the TBDPS ether. Thus, treatment of diol **14** with the TBDPS chloride gave the *sn*-1 TBDPS ether **15**. Deoxyfluorination of **15** gave good yields of the 2-fluorinated product **16**. Deprotection of ether **16** with TBAF in THF gave alcohol **17**, which was esterified with either oleic or palmitic acids as described above to give the target protected LPA derivatives **18a** and **18b**. Deprotection of the phosphotriester with bromotrimethylsilane afforded the desired fluorinated LPA analogues **2a** and **2b**. Similarly, the enantiomers **2c** and **2d** were synthesized from (*S*)-isopropylideneglycerol **5**.

1-fluoro-3,4-epoxy-butylphosphonate **22** (IUPAC numbering) was prepared by addition of iodofluoromethylene-phosphonate **20** to allyl alcohol and subsequent

base-induced cyclization of the iodohydrin **21** to epoxide **22** (Figure 13). The HKR reaction, using two enantiomeric cobalt salen complexes **23** as catalysts, would be used for kinetic resolution of terminal epoxide of **22** to obtain enantiomerically-enriched diols **24a** and **24b**. These diols in turn would be mono-acylated to give the corresponding enantiomeric α-monofluoromethylene phosphonate LPA analogues **3**.

Figure 13 shows the final synthetic route for these analogues. First, iodomonofluoromethyl phosphonate **20** was prepared in good yield from commercially-available diethyl dibromofluoromethyl phosphonate **19** by tributylphosphine reduction and iodine quench of the intermediate zinc species. Next, the tetrakis(triphenylphosphine)-palladium-catalyzed addition of phosphonate **20** to allyl alcohol in hexane gave the corresponding iodohydrin **21** in 79% yield. Treatment of the iodohydrin with dilute K_2CO_3/MeOH solution for 5 min at rt provided the desired epoxide **22** in good yield (72%). It is important to note that the racemic epoxide is also a mixture of fluorine epimers at C-1, as demonstrated by the two equal multiplets in the ^{19}F-NMR spectra of this and subsequent intermediates. Next, reaction of racemic epoxide **22** with 0.45 eq of H_2O in a min volume of THF, in the presence of 1.0 mol% of (*R,R*)-**23**-OAc gave diol **24a** in 90% ee and 73% isolated yield. Similarly, catalyst (*S,S*)-**23**-OAc provided the opposite configuration of diol **24b** in 89% ee and 90% yield.

The epoxide and diol were readily separated by flash chromatography, providing a further extension of the scope of the HKR process, which was previously employed to make the difluoromethylene phosphonates. Each diol was isolated as an inseparable, equimolar mixture of two diastereomers epimeric at C-1. For initial assessment of biological activity, the separation of this epimeric mixture at the C-1 phosphonate methylene was not required.

Regioselective acylation of the primary hydroxyl of diols **24** was readily accomplished (Figure 14). Note that the numbering employed henceforth for the phosphonate LPA analogues **24**, **25**, **26**, and **3** employs the *sn*-glycerol nomenclature

for clarity of comparison with other LPA derivatives. Thus, treatment of **24a** with 0.95 eq of oleic acid and 1.2 eq DCC and DMAP in CH_2Cl_2 at 0 °C gave **26aa** in 42% yield after chromatography to remove a small amount of diester. The corresponding palmitate **26ab** was similarly produced, as were the enantiomeric oleate **26ba** and palmitate **26bb**. Finally, LPA analogues **3** were obtained by dealkylation of the diethyl phosphonates **26** with excess bromotrimethylsilane (10.0 eq) for 8 h at rt.

Since we were unable to separate the diastereomeric 1-fluoro-3-hydroxyl isomers of compounds **24, 26,** or **3,** we selected an alternative approach to prepare a diastereomerically enriched α-monofluorinated phosphonate. For this synthesis, (2*S*)-1,2,4-butanetriol **27** was chosen as the commercially-available chiral starting material. Protection as the isopropylidene acetal followed by oxidation with PDC gave aldehyde **28**. The Pudovik reaction was then employed to introduce the C-P bond. Thus, the anion of diethyl phosphite was added to aldehyde **28** at -20 °C to give two chromatographically inseparable, α-hydroxyl phosphonates **29,** in modest overall yield. This addition reaction occurred without diastereoselectivity, since two single sharp resonances at 25.37 and 24.47 ppm of equal intensity were observed in the ^{31}P-NMR spectrum. This diastereomeric mixture was treated directly with DAST, which gave a pair of diastereomers in a 6.3:1 ratio as determined by both observed ^{31}P NMR and ^{19}F NMR in modest yield. After deprotection by acid hydrolysis and selective esterification, phosphonate **26aa** was obtained in > 89% de. Finally, TMSBr deprotection give the finally product **3aa** showing > 89% de (Figure 15). As no reference materials are available, and NMR methods failed to define the relative geometries of the C-H bonds at C-1 and C-3, we cannot assign the absolute configuration at C-1 to this predominant stereoisomer.

The preparation of receptor-specific agonists and antagonists for LPA receptors is an active area of ligand design. Structure-activity studies have demonstrated that analogues **31**and **32** (Figure 16), lacking the 2-hydroxy group and structurally different analogues, such as the *N*-palmitoylserine and *N*-palmitoyltyrosine phosphoric acids **33** and **34** (Figure 16), are potent competitive

antagonists of LPA receptor function in *Xenopus* oocytes. However, thus far, a comprehensive analysis of fluorinated LPA analogues as selective agonists or antagonists for individual LPA receptors has not yet been reported. The monofluorinated analogues described herein provide a set of ligands to perform this comprehensive analysis.

Preliminary results indicate that compounds **1a, 1b** and **2a-2d** were all able to activate platelets. Moreover, compounds **1a** and **1b** were found to be partial agonists of the (18:1) LPA pain response and compound **1c** was found to be somewhat more potent than natural 18:1 LPA on the LPA_3 receptor. However, analogues **1a, 1b** and **2a-2d** failed to show either significant agonist or antagonist activity when tested in insect cells expressing LPA_1, LPA_2, or LPA_3 receptors. Interestingly, monofluorinated *sn*-1 analogues **2a-2d** were essentially equipotent with *sn*-1-oleoyl-LPA for the activation of the PPARγ nuclear receptor[5]. Thus, preliminary data demonstrate that particular fluorine substitutions can give selective agonists for LPA receptors, and that biological responses show both regioselectivity and enantioselectivity relative to the placement of the acyloxy and fluoro substituents. Most importantly, the α-monofluoromethylene-substituted LPA analogue **3aa** was 1000-fold more potent than natural 18:1 LPA on the LPA_3 receptor. This response was also enantiospecific, clearly indicating that the α-fluorophosphonates are structurally informative and receptor-selective mimics for phosphate in LPA. The full biological data will be reported in due course.

Ligand recognition by GPCRs, as well as substrate recognition by enzymes, generally shows a strong preference for the naturally-occurring enantiomer. However, recognition of LPA by its receptors is an exception, as both the natural L(*R*) and unnatural D(*S*) stereoisomers of LPA have been reported to be equally active in selected bioassays. In contrast to the enantiomers of native LPA, preliminary data for fluorinated LPA analogues show that they are recognized in a stereoselective manner. For example, **1c** (*S*) is approximately 100-fold more potent than **1a** (*R*) on LPA_3 and **3aa** (*S*) is similarly 100-fold more potent than **3ab** (*R*). This distinction between LPA

and the fluorinated derivatives raises the intriguing possibility that these analogues may interact with the ligand-binding pocket of LPA receptors in a manner different from LPA.

General Procedures. Except where noted, all reagents were purchased commercially. Solvents were of reagent grade and were distilled before use: THF was dried by distillation from sodium-benzophenone ketyl and methylene chloride was distilled from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. NMR spectra were recorded on 400 MHz (^1H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F), at 25 °C. Chemical shifts are reported relative to those of internal chloroform ($\delta_H = 7.24$), methanol ($\delta_H = 4.78$), or tetramethylsilane ($\delta_H = 0.00$) for ^1H; chloroform ($\delta_C = 77.0$) or methanol ($\delta_C = 49.0$) for ^{13}C; $CFCl_3$ for ^{19}F ($\delta_F = 0.00$); 85% H_3PO_4 ($\delta_P = 0.00$) as external standard. Optical rotations were obtained at ambient temperature.

Dimethyl 1,2-(*S*)-isopropylidene-*sn*-glycerol-3-phosphate 6. *t*-BuOK (1.274 g, 11.35 mmol) was added to a stirred solution of (*R*)-isopropylideneglycerol (1.00 g, 7.57 mmol) and dimethyl chlorophosphate (1.367 g, 9.46 mmol) in CH_2Cl_2 (25 mL), stirred at rt for 1 h (complete by TLC). A saturated aq solution of NH_4Cl 40 mL was added, stirred 10 min, and the aq phase was extracted three times with CH_2Cl_2 (30 mL); the organic solution was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified on silica gel by elution with diethyl ether to give 1.62 g (6.75 mmol, 92% yield, $R_f = 0.30$, diethyl ether) of pure product as a colorless oil. $\delta_H(CDCl_3)$: 4.22 (m, 1H), 3.95 (m, 4H), 3.69 (s, 3H), 3.66 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H). $\delta_H(CDCl_3)$: 106.69 (s), 73.88 (d, $J = 7.6$ Hz), 67.36 (d, $J = 5.3$ Hz), 65.84 (s), 54.23 (d, $J = 3.8$ Hz), 26.51 (s), 25.06 (s). $\delta_P(CDCl_3)$: 2.23 (s). $[\alpha]^{20}_D = +2.28°$ (c = 2.08, MeOH).

Dimethyl (2S)-1,2-di(*tetra*-butyldimethylsilyl)-*sn*-glycerol-3-phosphate 8. TsOH (54 mg, 0.283 mmol, 0.10 eq) was added to a solution of 6 (0.678 g, 2.825 mmol) in MeOH (10 mL), and the solution was stirred at rt for 24 h. After addition of NEt_3 (0.1 mL), the solvent was removed under reduced pressure. Following addition of

anhydrous DMF (3 mL), imidazole (0.577 g, 8.475 mmol, 3.0 eq) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (1.107 g, 7.345 mmol, 2.8 eq.), the reaction mixture was stirred at rt for an additional 36 h. The solution was diluted with water (15 mL) and ethyl acetate (20 mL), and the aqueous layer was separated and extracted three times with ethyl acetate (30 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue was purified on silica gel (*n*-hexane/ethyl acetate 4:1, R_f= 0.13) to afford 0.804 g (1.879 mmol, 67%) of a colorless liquid . $\delta_H(CDCl_3)$: 4.08 (m, 1H), 3.89 (m, 1H), 3.80 (m, 1H), 3.73 (d, J= 1.2 Hz, 3H), 3.70 (d, J= 1.2 Hz, 3H), 3.51 (d, J= 5.2 Hz, 3H), 0.84 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). $\delta_C(CDCl_3)$: 84.77 (d, J= 6.1 Hz), 77.50 (d, J= 7.6 Hz), 74.36 (d, J= 6.2 Hz), 69.50 (s), 67.52 (d, J= 4.5 Hz), 59.69 (d, J= 6.3 Hz), 31.34 (s), 31.20 (s), 31.22 (s), 23.75 (s), 23.57 (s), 0.77 (s), 0.68 (s), 0.02 (s), 0.00 (s). $\delta_P(CDCl_3)$: 2.42 (s). MS (CI) *m/z* 429.1 (M^++1, 100.00). HRMS $C_{17}H_{42}PSi_2O_6$, Found: 429.2244; Calcd for 429.2230. $[\alpha]^{20}_D$ = +0.18° (c = 2.25, MeOH).

Dimethyl (2S)-(*tetra*-butyldimethylsilyl)-*sn*-glycerol-3-phosphate 9. The HF·pyridine complex (70%, 0.31 mL) was added to a mixture of pyridine (1.40 mL) and a solution of the bis-TBDMS ether **8** (0.759 g, 1.773 mmol) in THF (10 mL). The reaction mixture was stirred for 24 h. After completion of the reaction (TLC), the solution was diluted with ethyl acetate (50 mL), washed with saturated NaCl solution (5 mL), and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was purified on silica gel (ethyl acetate, R_f= 0.23) to afford a colorless liquid 0.254 g (0.814 mmol, 46%). $\delta_H(CDCl_3)$: 3.93 (m, 2H), 3.82 (m, 1H), 3.69 (d, J= 1.2 Hz), 3.66 (d, J= 1.2 Hz, 3H), 3.52 (dd, J= 8.4, 4.4Hz, 2H,), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). $\delta_C(CDCl_3)$: 76.06 (d, J= 7.6 Hz), 72.40 (d, J= 6.1 Hz), 67.93 (s), 59.29 (d, J= 6.1 Hz), 30.57 (s), 22.91 (s), 0.11 (s), 0.00 (s). $\delta_P(CDCl_3)$: 2.788 (s). MS (CI) *m/z* 315.1 (M^++1, 100.00). HRMS $C_{11}H_{28}SiPO_6$, Found: 315.1412; Calcd for 315.1414. $[\alpha]^{20}_D$ = +0.28° (c = 1.08, MeOH).

1-Phospho-2(S)-(*tetra*-butyldimethylsilyl)-3-fluorine-propane-1,2-diol dimethyl ester 10. To a mixture of (0.035 g, 0.220 mmol) of DAST and 2 mL of dry CH_2Cl_2 at -78 °C was added dropwise a solution of (0.049 g, 0.157 mmol) alcohol in 1 mL of dry CH_2Cl_2. The mixture was stirred at -78 °C for 1h, at rt for an additional 1 h. To the mixture was added 0.2 mL of methanol followed by neutralization with solid $NaHCO_3$. After concentration in vacuo, the residue was purified on silica gel (hexane-ethyl acetate, 1:1, R_f = 0.25) to afford 0.026 g. (0.083 mmol, 53%) as a colorless oil. $\delta_H(CDCl_3)$: 4.35 (ddd, 1H), 4.24 (ddd, 1H), 4.02-3.86 (m, 3H), 3.69 (d, J = 1.2 Hz, 3H), 3.66 (d, J = 1.2 Hz, 3H), 0.79 (s, 9H), 0.05 (s, 6H). $\delta_C(CDCl_3)$: 88.46 (d, J = 172.6 Hz), 74.76 (dd, J = 20.7, 8.5 Hz), 72.26 (t, J = 6.5 Hz), 59.31 (d, J = 7.6 Hz), 30.55 (s), 22.98 (s), 0.00 (s). $\delta_P(CDCl_3)$: 2.252 (s). $\delta_F(CDCl_3)$: 230.50 (td, J = 47.0, 20.7 Hz). MS (CI) *m/z* 317.1 (M^++1, 100.00). HRMS $C_{11}H_{27}FSiPO_5$, Found: 317.1344; Calcd for 317.1349. $[\alpha]^{20}_D$ = +0.23° (c = 0.33, MeOH).

1-Phospho-2(*S*)-(oleoyl)-3-fluorine-propane-1,2-diol dimethyl ester 12a. A solution of **10** (18 mg, 0.058 mmol) in THF (2 mL) was treated consecutively with acetic acid (13 μL, 0.231 mmol) and tetrabutylammoniumfluoride trihydrate (73 mg, 0.231 mmol) at rt. After stirring for 18 h, the reaction was complete (TLC control), the solvent was evaporated under reduced pressure and the crude product was purified on a short column of silica gel to afford a colorless liquid. To the crude alcohol **11** and 42 mg, 47 μL, 0.147 mmol of oleic acid in dry CH_2Cl_2 (1 mL) at rt was added dropwise a solution of DCC (30 mg, 0.147 mmol) and DMAP (6 mg, 0.048 mmol) in dry CH_2Cl_2 (1 mL). The solution was stirred at rt for 18 h, filtered, concentrated in vacuo, and the residue was purified on silica gel (*n*-hexane-ethyl acetate 1:1, R_f = 0.28) to afford 12 mg of a waxy solid (0.026 mmol, 45%). $\delta_H(CDCl_3)$: 5.28 (m, 2H), 5.14 (dm, J = 20.8 Hz, 1H), 4.51 (dd, J = 46.8, 4.0 Hz, 2H), 4.15 (m, 2H), 3.73 (d, J = 2.4 Hz, 3H), 3.70 (d, J = 2.4 Hz, 3H), 2.30 (t, J = 7.2 Hz, 2H), 1.90 (m, 4H), 1.56 (m, 4H), 1.14 (m, 20H), 0.81 (t, J = 6.4 Hz, 3H). $\delta_C(CDCl_3)$: 173.00 (s), 130.26 (s), 129. 93 (s), 80.22 (d, J = 172.0 Hz), 70.29 (d, J = 28.6 Hz), 64.64 (t, J = 6.5 Hz), 54.74 (s), 54.68 (s), 34.32 (s), 34.17 (s), 32.12 (s), 29.98 (s), 29.90 (s), 29.53 (s),

29.36 (s), 29.30 (s), 29.24 (s), 27.44 (s), 27.38 (s), 25.84 (s), 25.16 (s), 25.01 (s), 22.89 (s), 14.32 (s). $\delta_P(CDCl_3)$: 2.185 (s). $\delta_F(CDCl_3)$: -234.50 (td, J = 47.0, 20.7 Hz). MS (CI) *m/z* 467.0, (M^++1, 100.00), 341.2 (M^+-OPO(OMe)$_2$, 56.20). HRMS $C_{23}H_{45}FPO_6$, Found: 467.2921; Calcd for 467.2904. $[\alpha]^{20}_D$ = +0.69° (c = 0.36, MeOH).

1-Phospho-2(*S*)-(palmitoyl)-3-fluorine-propane-1,2-diol Dimethyl Ester 12b. A solution of **10** (22 mg, 0.071 mmol) in THF (2 mL) was treated consecutively with acetic acid (16 μL, 0.282 mmol) and tetrabutylammoniumfluoride trihydrate (89 mg, 0.282 mmol) at rt. The crude alcohol 11 was directly esterified with palmitic acid (following the protocol above for **12a**) and purified on silica gel (*n*-hexane-ethyl acetate 1:1, R_f = 0.28) to afford 11 mg of a waxy solid (0.025 mmol, 35%). $\delta_H(CDCl_3)$: 5.20 (dm, J = 21.0 Hz, 1H), 4.57 (dd, J = 46.8, 4.0 Hz, 2H), 4.25 (m, 2H), 3.79 (d, J = 2.8 Hz, 3H), 3.76 (d, J = 2.4 Hz, 3H), 2.36 (t, J = 9.6 Hz, 2H), 1.93 (m, 2H), 1.62 (m, 4H), 1.24 (m, 20H), 0.87 (t, J = 9.6 Hz, 3H). $\delta_C(CDCl_3)$: 173.0 (s), 80.84 (d, J = 173.4 Hz), 70.27 (d, J = 7.64 Hz), 70.07 (d, J = 7.4 Hz), 64.64 (t, J = 6.7 Hz), 54.74 (s), 54.68 (s), 29.88-29.86 (m), 29.81 (s), 29.57 (s), 29.45 (s), 29.27 (s). $\delta_P(CDCl_3)$: 2.171 (s). $\delta_F(CDCl_3)$: -234.49 (td, J = 47.0, 21.0 Hz). MS (CI) *m/z* 441.3 (M^++1, 20.84), 225, (M^+-H_2O-$C_{12}H_{25}$, 100.00). HRMS $C_{21}H_{43}FPO_6$, Found: 441.2790; Calcd for 441.2781. $[\alpha]^{20}_D$ = +0.91° (c = 0.29, MeOH).

1-Phospho-2(*S*)-(oleoyl)-3-fluorine-propane-1,2-diol 1a. Thoroughly dried ester **12a** (8 mg, 0.017 mmol, 5 h under high vacuum) was dissolved in dry methylene chloride (1 mL) at rt; bromotrimethylsilane (9 μL, 0.052 mmol) was added via syringe and the reaction was stirred for 4 h. When TLC indicated that all of the reactant had been consumed, the solvent was removed under reduced pressure and the residue dried in vacuo. The residue was dissolved in 95% methanol (1 mL) for 1 h, the solvent was then removed under reduced pressure and the product dried in vacuo to give 6 mg of a colorless oil (CH_2Cl_2:CH_3OH:H_2O = 20:10:1, R_f = 0.39 , 0.014 mmol, 82% yield.). $\delta_H(CD_3OD)$: 5.24 (m, 2H), 5.11 (dm, J = 20.4 Hz, 1H,), 4.49 (dd, J = 47.2, 4.8 Hz, 2H), 4.03 (m, 2H), 2.29 (t, J = 7.6 Hz, 2H), 1.93 (m, 4H), 1.61-1.54 (m,

4H), 1.20 (m, 17H), 0.81 (t, J = 6.4 Hz, 3H). δ_C(CD_3OD): 173.80 (s), 130.86 (s), 130.53 (s), 80.72 (d, J = 171.9 Hz), 70.79 (d, J = 28.4 Hz), 65.09 (t, J = 6.5 Hz), 34.75 (s), 34.60 (s), 33.72 (s), 33.55 (s), 31.87 (s), 29.65 (s), 29.60 (s), 29.41 (s), 29.25 (s), 29.15 (s), 29.08 (s), 28.98 (s), 28.91 (s), 26.93 (s), 14.35 (s). δ_P(CD_3OD): 0.843 (s). δ_F(CD_3OD): -235.96 (td, J = 47.0, 20.7 Hz). m/z 438.0 (M^+, 0.30), 314.2, (M^+-$OPO(OH)_2$, 100.00), 157, (M^+-OCOR, 62.91). MS (CI) *m/z* 439.3 (M^++1, 45.34). HRMS, M^++1, Found: 439.2634. Calcd for $C_{21}H_{41}FO_6P$, 439.2625 $[\alpha]^{20}_D$ = +0.57° (c = 0.12, MeOH).

1-Phospho-2(*S*)-(palmitoyl)-3-fluorine-propane-1,2-diol 1b. Deprotection of **12b** (11 mg, 0.025 mmol, 5 h drying at 0.01 mg Hg) was conducted as described above for **12a** to give 6 mg of phosphate **1b** as a colorless oil (CH_2Cl_2:CH_3OH:H_2O = 20:10:1, R_f = 0.37, 0.019 mmol, 78% yield). δ_H(CD_3OD): 5.22 (dm, J = 21.0 Hz, 1H), 4.58 (dd, J = 47.2, 3.2 Hz, 2H), 4.25 (m, 2H), 2.36 (t, J = 9.6 Hz, 2H), 1.93 (m, 2H), 1.76 (m, 2H), 1.62 (m, 4H), 1.29 (m, 18H), 0.87 (t, J = 6.8 Hz, 3H). δ_C(CD_3OD): 173.40 (s), 81.24 (d, J = 173.3 Hz), 70.67 (d, J = 7.5 Hz), 70.47 (d, J = 7.4 Hz), 64.95 (t, J = 6.6 Hz), 32.78 (s), 32.14 (s), 29.93 (s), 29.88 (s), 29.71 (s), 29.59 (s), 25.26 (s), 25.00 (s), 24.63 (s), 22.91 (s), 14.32 (s). δ_P(CD_3OD): 1.742 (s). δ_F(CD_3OD): -234.63 (td, J = 46.0, 21.0 Hz). MS (CI) *m/z* 413.3 (M^++1, 51.22). HRMS, M^++1, Found: 413.2479. Calcd for $C_{19}H_{39}FO_6P$, 413.2468 $[\alpha]^{20}_D$ = +0.81° (c = 0.14, MeOH).

1-Phospho-2(*S*)-(oleoyl)-3-fluorine-propane-1,2-diol 1c. Colorless oil, δ_H(CD_3OD): 5.24 (m, 2H), 5.11 (dm, J = 20.4 Hz, 1H,), 4.49 (dd, J = 47.2, 4.8 Hz, 2H), 4.03 (m, 2H), 2.29 (t, J = 7.6 Hz, 2H), 1.93 (m, 4H), 1.61-1.54 (m, 4H), 1.20 (m, 17H), 0.81 (t, J = 6.4 Hz, 3H). δ_C(CD_3OD): 173.80 (s), 130.86 (s), 130.53 (s), 80.72 (d, J = 171.9 Hz), 70.79 (d, J = 28.4 Hz), 65.09 (t, J = 6.5 Hz), 34.75 (s), 34.60 (s), 33.72 (s), 33.55 (s), 31.87 (s), 29.65 (s), 29.60 (s), 29.41 (s), 29.25 (s), 29.15 (s), 29.08 (s), 28.98 (s), 28.91 (s), 26.93 (s), 14.35 (s). δ_P(CD_3OD): 0.840 (s). δ_F(CD_3OD): -235.96 (td, J = 46.6, 20.6 Hz). $[\alpha]^{20}_D$ = -0.71° (c = 0.29, MeOH).

Dimethyl 1-(*tetra*-butyldiphenylsilyl)-2-(*R*)-*sn*-glycerol-3-phosphate 15. TsOH

(0.594 g, 3.0 mmol, 0.15 eq) was added to a solution of (4.80 g, 20.00 mmol) in MeOH (100 mL), and the solution was stirred at rt for 24 h. Following addition of solid $NaHCO_3$, the mixture was filtered, concentrated in vacuo, and purified on silica gel (methanol-ethyl acetate 1:5, $R_f = 0.26$) to afford 3.64 g (18.2 mmol, 91%) of diol **14** as a colorless liquid. To a solution of the crude diol **14** (3.45 g, 17.25 mmol) in anhydrous DMF (120 mL), was added imidazole (3.41 g, 50.03 mmol, 2.9 eq) and *tert*-butyldiphenylsilyl chloride (TBDBSCl) (6.16 g, 22.43 mmol, 1.3 eq). The reaction mixture was stirred at 0 °C for 8 h, then at rt for 12 h. The solution was diluted with ethyl acetate (100 mL), and the solution was washed with saturated NH_4Cl aq solution and brine. After drying with anhydrous Na_2SO_4, the organic layer was concentrated in vacuo and purified on silica gel (ethyl acetate, $R_f = 0.48$) to afford 5.10 g of a colorless liquid (11.68 mmol, 68%). $\delta_H(CDCl_3)$: 7.65 (m, 4H), 7.36 (m, 6H), 4.16 (m, 2H), 3.93 (m,1H), 3.71 (d, $J = 3.0$ Hz, 3H), 3.68 (d, $J = 2.0$ Hz, 3H), 1.04 (s, 9H). $\delta_C(CDCl_3)$: 135.20 (s), 135.18 (s), 132.74 (s), 132.73 (s), 129.51 (s), 127.47 (s), 70.20 (d, $J = 6.1$ Hz), 68.52 (d, $J = 6.1$ Hz), 63.61 (s), 54.05 (dd, $J = 6.1$, 2.3 Hz), 26.49 (s), 18.88 (s). $\delta_P(CDCl_3)$: 2.869 (s). MS (CI) *m/z* 438.9 (M^++1, 20.62), 380.9 (M^+-C_4H_9, 39.84), 360.9 (M^+-C_6H_5, 100.00). HRMS, M^++1, Found: 439.1685. Calcd for $C_{21}H_{32}O_6PSi$, 439.1706. $[\alpha]^{20}_D = -0.77$ (c = 0.31, MeOH).

1-Phospho-2(*S*)-fluorine-3-(*tetra*-butyldiphenylsilyl)-propane-1,3-diol dimethyl ester 16. To a mixture of DAST (1.77 g, 10.96 mmol) and 50 mL of dry CH_2Cl_2 at -78 °C was added dropwise a solution of (4.00 g, 9.13 mmol) alcohol in 20 mL of dry CH_2Cl_2. The mixture was stirred at -78 °C for 1h, followed by 1 h at rt. The mixture was poured into a stirred mixture of saturated $NaHCO_3$ and ice chips, the extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The oil was purified on silica gel (hexane-ethyl acetate, 1:1, $R_f = 0.19$) on silica gel to afford 1.53 g (3.47 mmol, 38%) of **16** as a colorless liquid. $\delta_H(CDCl_3)$: 7.64 (m, 4H), 7.42 (m, 6H), 4.71 (dm, $J = 47.6$ Hz, 1H), 4.30 (dm, $J = 23.6$ Hz, 2H), 3.83 (m, 2H), 3.76 (d, $J = 2.4$ Hz, 3H), 3.68 (d, $J = 2.4$ Hz, 3H), 1.04 (s, 9H). $\delta_C(CDCl_3)$: 135.55 (s), 135.49 (s), 132.79 (s), 132.67 (s),

129.90 (s), 127.81 (s), 127.79 (s), 91.17 (dd, J = 177.2, 6.9 Hz), 66.33 (dd, J = 23.7, 5.3 Hz), 62.27 (d, J = 25.3 Hz), 54.40 (d, J = 6.1 Hz), 26.68 (s), 19.19 (s).$\delta_F(CDCl_3)$: -196.16 (1F, m). $\delta_P(CDCl_3)$: 2.278 (s). MS (CI) *m/z* 383.0 (M^+-C_4H_9, 29.86), 363.0 (M^+-C_6H_5, 100.00). HRMS, M^+-C_4H_9, Found: 383.0875. Calcd for $C_{17}H_{21}FO_5PSi$, 383.0880. $[\alpha]^{20}_D$ = -4.88° (c = 0.42, MeOH).

1-Phospho-2(*S*)-fluorine-propane-1,3-diol Dimethyl Ester 17. A solution of **16** (860 mg, 1.972 mmol) in THF (50 mL) was treated consecutively with acetic acid (0.46 mL, 7.888 mmol) and tetrabutylammoniumfluoride trihydrate (2.489 g, 7.888 mmol) at rt. After stirring for 16 h, the reaction was complete (TLC), and the mixture was concentrated and passed through a silica column (ethyl acetate, R_f = 0.20) to afford 0.342 g (1.693 mmol, 86%) of **17** as a colorless liquid. $\delta_H(CDCl_3)$: 4.67 (dm, J = 48.0 Hz, 1H), 4.23 (ddd, J = 22.4, 7.6, 4.4 Hz, 2H), 3.77 (dm, J = 19.6 Hz, 2H), 3.75 (d, J = 2.0 Hz, 3H), 3.72 (d, J = 2.0 Hz, 3H), 3.48 (br, 1H). $\delta_C(CDCl_3)$: 91.32 (dd, J = 174.8, 6.1 Hz), 66.02 (dd, J = 23.7, 5.3 Hz), 60.53 (d, J = 23.8 Hz), 54.54 (dd, J = 6.1, 3.8 Hz). $\delta_F(CDCl_3)$: -197.66 (1F, m). $\delta_P(CDCl_3)$: 2.453 (s). MS (CI) *m/z* 203.1 (M^++1, 100.00). HRMS, M^++1, Found: 203.0476. Calcd for $C_5H_{12}FO_5P$, 203.0485.

1-Phospho-2(*R*)-fluorine-3-(oleoyl)-propane-1,3-diol Dimethyl Ester 18a. To a solution of crude alcohol **17** (73 mg, 0.361 mmol) with oleic acid (113 mg, 0.397 mmol) in dry CH_2Cl_2 (3 mL) at rt was added dropwise a solution of DCC (112 mg, 0.542 mmol) and DMAP (27 mg, 0.217 mmol) in dry CH_2Cl_2 (3 mL). The solution was stirred at rt for 16 h and filtered, the solvent removed, and the residue was purified on silica gel (n-hexane-ethyl acetate 1:2, R_f= 0.30) to afford 162 mg (0.347 mmol, 96%) of **18a** as a waxy solid. $\delta_H(CDCl_3)$: 5.28 (m, 2H), 4.80 (dm, J = 47.6 Hz, 1H), 4.24 (m, 4H), 3.74 (s, 3H), 3.72 (s, 3H), 2.86 (t, J = 7.2 Hz), 1.94 (m, 4H), 1.56 (m, 2H), 1.22 (m, 20H), 0.81 (t, J = 8.0 Hz, 3H). $\delta_C(CDCl_3)$: 173.07 (s), 129.87 (s), 129.57 (s), 88.67 (dd, J = 178.0, 7.6 Hz), 65.77 (dd, J = 24.5, 5.3 Hz), 61.97 (d, J = 23.7 Hz), 54.39 (d, J = 6.1 Hz), 33.80 (s), 31.77 (s), 29.63 (s), 29.54 (s), 29.38 (s), 29.18 (s), 29.00 (s), 28.94 (s), 28.92 (s), 27.07 (s), 27.02 (s), 24.67 (s), 22.54 (s),

13.96 (s). $\delta_F(CDCl_3)$: -195.98 (1F, m). $\delta_P(CDCl_3)$: 2.151 (s). MS (CI) *m/z* 467.4 (M^++1, 100.00), 341.3 (M^+-$C_2H_6PO_4$, 32.11). HRMS, M^++1, Found: 467.2891. Calcd for $C_{23}H_{45}FO_6P$, 467.2938. $[\alpha]^{20}_D$ = -1.92° (c = 2.52, MeOH).

1-Phospho-2(*R*)-fluorine-3-(palmitoyl)-propane-1,3-diol Dimethyl Ester 18b. The same procedure was followed as for **18a** to give **18b** as a waxy solid (*n*-hexane-ethyl acetate 1:2, R_f = 0.30; 139 mg, 0.316 mmol, 91%). $\delta_H(CD_3Cl)$: 4.77 (dm, *J* = 48.0 Hz, 1H), 4.17 (m, 4H), 3.77 (s, 3H), 3.68 (s, 3H), 2.26 (t, J = 7.6 Hz, 2H), 1.53 (m, 2H), 1.16 (m, 24H), 0.78 (t, *J* = 6.4 Hz, 3H). $\delta_C(CD_3OD)$: 173.43 (s), 88.57 (dd, *J* = 178.7, 7.6 Hz), 65.87 (dd, *J* = 23.8, 5.4 Hz), 61.92 (d, *J* = 23.8 Hz), 54.43 (d, *J* = 6.1 Hz), 33.77 (s), 31.72 (s), 29.49 (s), 29.45 (s), 29.39 (s), 29.25 (s), 29.16 (s), 29.03 (s), 28.89 (s), 24.62 (s), 22.48 (s), 13.87 (s). $\delta_F(CD_3OD)$: -196.11 (1F, m). $\delta_P(CD_3OD)$: 1.977 (s). MS (CI) *m/z* 441.3 (M^++1, 100.00), 315.3 (M^+-$C_2H_6PO_4$, 38.53). HRMS, M^++1, Found: 441.2770. Calcd for $C_{21}H_{43}FO_6P$, 441.2781. $[\alpha]^{20}_D$ = -1.25° (c = 1.25, $CHCl_3$).

1-Phospho-2(*S*)-fluorine-3-oleoyl-propane-1,3-diol 2a. Following the same procedure used above for **1a** afforded analogue **2a** as a white solid in 86% yield. $\delta_H(CD_3OD/CDCl_3, 2/1)$: 5.32 (m, 2H), 4.82 (dm, *J* = 48.0 Hz, 1H), 4.37 (m, 2H), 4.05 (ddd, *J* = 48.0 , 5.8, 5.2 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 3H), 2.00 (m, 4H), 1.62 (m, 2H), 1.29 (m, 20H), 0.87 (t, *J* = 6.4 Hz, 3H). $\delta_C(CD_3OD/CDCl_3, 2/1)$: 174.10 (s), 129.86 (s), 129.69 (s), 90.70 (dd, *J* = 175.0, 7.6 Hz), 64.47 (dd, *J* = 24.5, 5.4 Hz), 64.13 (d, *J* = 22.2 Hz), 34.63 (s), 32.64 (s), 30.45 (s), 30.40 (s), 30.22 (s), 30.03 (s), 29.97 (s), 29.89 (s), 29.79 (s), 27.82 (s), 27.80 (s), 25.57 (s), 23.35 (s), 14.37 (s). $\delta_F(CD_3OD/CDCl_3, 2/1)$: -196.35 (1F, m). $\delta_P(CD_3OD/CDCl_3, 2/1)$: 2.145 (s). MS (CI) *m/z* 437.2 (M^++1-2Na^+, 86.37). HRMS, M^++1-2Na^+, Found: 437.2429. Calcd for $C_{21}H_{39}FO_6P$, 437.2390. $[\alpha]^{20}_D$: = +0.57° (c = 0.58, MeOH).

1-Phospho-2(*S*)-fluorine-3-palmitoyl-propane-1,3-diol 2b was obtained similarly as a white solid in 91% yield. $\delta_H(D_2O/CD_3OD)$: 4.81 (dm, *J* = 48.8 Hz, 1H), 4.24 (dd, *J* = 7.6, 6.4 Hz, 2H), 3.87 (dm, *J* = 5.7 Hz, 2H), 2.27 (t, *J* = 5.2 Hz, 2H), 1.49 (m, 2H),

1.16 (m, 24H), 0.76 (t, J = 6.0 Hz, 3H). $\delta_C(D_2O/CD_3OD)$: 173.43 (s), 88.57 (dd, J = 178.7, 7.6 Hz), 65.87 (dd, J = 23.8, 5.4 Hz), 61.92 (d, J = 23.8 Hz), 33.77 (s), 31.72 (s), 29.49 (s), 29.45 (s), 29.39 (s), 29.25 (s), 29.16 (s), 29.03 (s), 28.89 (s), 24.62 (s), 22.48 (s), 13.87 (s). $\delta_F(D_2O/CD_3OD)$: -194.87 (1F, m). $\delta_P(D_2O/CD_3OD)$: 4.325 (s). MS (CI) *m/z* 441.4 (M^++1-2Na^+, 100.00). HRMS, M^++1, Found: 411.2307. Calcd for $C_{19}H_{43}FO_6P$, 411.2312. $[\alpha]^{20}_D$ = -5.00° (c = 0.08, MeOH/H_2O, 1/1, v/v).

1-Phospho-2(R)-fluorine-3-oleoyl-propane-1,3-diol 2c was obtained similarly as a white solid. $[\alpha]^{20}_D$: = -0.69° (c = 0.45, MeOH).

1-Phospho-2(R)-fluorine-3-palmitoyl-propane-1,3-diol 2d was obtained similarly as a white solid. $[\alpha]^{20}_D$ = -4.51° (c = 0.24, MeOH:H_2O = 1:1, v/v).

Diethyl [1-fluoro-3,4-epoxy-butyl]phosphonate 22. K_2CO_3 (0.375 g, 2.712 mmol) was added to a solution of iodohydrin **21** (0.160 g, 0.452 mmol) in MeOH (20 mL). The reaction mixture was stirred for 10 min at rt, diluted with water, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to give 69 mg. (0.307 mmol, 68%, *n*-hexane-ethyl acetate = 1:2, R_f = 0.21) of epoxide **22** as a colorless liquid. $\delta_H(CDCl_3)$: 4.94-4.70 (m, 1H), 4.18-4.09 (m, 4H), 3.09 (m, 1H), 2.79 (t, J = 4.8 Hz, 0.5H), 2.72 (t, J = 4.4 Hz, 0.5H), 2.50 (m, 1H), 2.21-2.08 (m, 2H), 1.28 (m, 6H). $\delta_C(CDCl_3)$: 86.85 (dd, J = 172. 6, 148.0 Hz), 86.32 (dd, J = 172. 6, 148.0 Hz), 63.24 (dd, J = 7.6, 3.8 Hz), 62.88 (dd, J = 10.8, 6.1 Hz), 48.40 (dd, J = 14.6, 3.8 Hz), 48.17 (dd, J = 16. 9, 3.8 Hz), 47.54 (s), 46.32 (s), 33.73 (dd, J = 20.6, 1.5 Hz), 32.79 (dd, J = 19.9, 1.5 Hz), 16.33 (d, J = 3.0 Hz), 16.27 (d, J = 3.1 Hz). $\delta_F(CDCl_3)$: -207.82 (0.5F, m), -211.22 (0.5F, m). $\delta_P(CDCl_3)$: 18.02 (0.5d, J = 73.8 Hz), 17.97 (0.5d, J = 75.0 Hz). MS (CI) *m/z* 227.1 (M^++1, 15.81), 203.1 (M^++1, 11.28). HRMS, M^++1, Found: 227.0836. Calcd for $C_8H_{17}FO_4P$, 227.0849.

Hydrolytic Kinetic Resolution of Epoxide 22. A 10-mL flask equipped with a stir bar was charged with (*R,R*)-**23** (26.7 mg, 43 μmol, 0.01 eq). The catalyst was dissolved in 0.4 mL of PhMe and treated with AcOH (10 μL, 0.177 mmol). The solution was allowed to stir at rt open to air for 30 min; the color changed from

orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in a solution of epoxide **22** (1.00 g, 4.425 mmol) and THF (150 μL) at rt, the reaction flask was cooled to 0 °C, and H_2O (36 μL, 1.991 mmol, 0.45 eq) was added dropwise over 5 min. The reaction was allowed to warm to rt while stirring for 14 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and the precipitate was removed by passage through Celite 351. Flash chromatography on silica gel afforded (*R*)-epoxide **25a** (0.485 g, 2.146 mmol, 97%, R_f= 0.32, CH_2Cl_2: CH_3OH = 20:1) and (*S*)-diol **24a** (0.394 g, 1.615 mmol, 73%, R_f= 0.34, CH_2Cl_2: CH_3OH = 10:1). The ee value of **24a** was 91%, which is obtained by conversion to the known[25] isopropylidene-protected ketal. A comparison of the reported optical rotation values was then made.

Diethyl [1-Fluoro-3(*S*), 4-dihydroxybutyl]phosphonate 24a was obtained as described above as a colorless liquid. $\delta_H(CDCl_3)$: 5.13-4.88 (m, 1H), 4.21-4.05 (m, 4H), 3.97-3.85 (br, 2H), 3.61-3.41 (m, 3H), 2.12-1.94 (m, 2H), 1.31 (m, 6H). $\delta_C(CDCl_3)$: 86.16 (dd, J= 171.0, 180.0 Hz), 85.54 (dd, J= 171.0, 180.0 Hz), 68.34 (dd, J= 9.3, 3.1 Hz), 67.23 (dd, J= 14.2, 1.8 Hz), 66.59 (s), 65.88 (s), 63.65 (d, J= 7.6 Hz), 63.44 (d, J= 6.8 Hz), 63.19 (d, J= 6.9 Hz), 63.12 (d, J= 6.1 Hz), 33.87 (d, J = 20.0 Hz), 33.68 (d, J= 19.1 Hz), 16.34 (d, J= 5.3 Hz), 16.29 (d, J= 4.6 Hz). $\delta_F(CDCl_3)$: -207.48 (0.5F, m), -211.53 (0.5F, m). $\delta_P(CDCl_3)$: 19.91 (0.5P, d, J= 75.0 Hz), 19.40 (0.5P, d, J= 76.1 Hz). MS (CI) *m/z* 245.2 (M^++1, 100.00), 231.1 (M^++2-CH_3, 3.27). HRMS, M^++1, Found: 245.0965. Calcd for $C_8H_{19}FO_5P$, 245.0954. $[\alpha]^{20}_D$ = -18.77 (c = 3.08, MeOH).

Diethyl [1-difluoro-3(*R*)-3,4-epoxy-butyl]phosphonate 25a. Recovered in resolved form as described above as a colorless liquid. $\delta_C(CDCl_3)$: 4.97-4.72 (m, 1H), 4.21-4.12 (m, 4H), 3.14-3.10 (m, 1H), 2.83 (t, J= 4.0 Hz, 0.5H), 2.75 (t, J= 4.0 Hz, 0.5H), 2.54 (m, 1H), 2.29-2.08 (m, 2H), 1.32 (m, 6H). $\delta_C(CDCl_3)$: 85.92 (dd, J= 180.9, 172.5 Hz), 86.17 (dd, J= 180.2, 172. 6 Hz), 63.35 (d, J= 3.1 Hz), 63.28 (d, J= 3.1 Hz), 63.00 (d, J= 4.6 Hz), 62.93 (d, J= 4.6 Hz), 48.49 (dd, J= 14.6, 3.8 Hz), 48.26 (dd, J= 17.6, 3.8 Hz), 47.63 (s), 46.41 (s), 37.80 (d, J= 19.8 Hz), 32.85 (d, J=

19.9 Hz), 16.40 (d, J = 12.4 Hz), 16.35 (d, J = 12.0 Hz). $\delta_F(CDCl_3)$: -207.73 (0.5F, m), -211.17 (0.5F, m). $\delta_P(CDCl_3)$: 18.07 (d, J = 73.8 Hz). $[\alpha]^{20}_D$ = +9.75 (c = 3.54, MeOH).

To obtain the enantiomeric diol **24b**, the enantiomeric catalyst was employed as follows. A 10-mL flask equipped with a stir bar was charged with (*S,S*)-**23** (20.3 mg, 34 □mol, 0.01 eq). The catalyst was dissolved in 0.4 mL of PhMe and treated with AcOH (7 μL, 0.134 mmol). The solution was allowed to stir at rt open to air for 30 min; the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in epoxide (0.758 g, 3.354 mmol) and THF (120 μL) at rt, the reaction flask was cooled to 0°C, and H_2O (27 μL, 1.509 mmol, 0.45 eq) was added dropwise over 5 min. The reaction was allowed to warm to rt, stirred for 14 h, concentrated, and purified on silica gel to give (*S*)-epoxide **25b** (0.369 g, 1.631 mmol, 98%) and (*S*)-diol **24b** (0.375 g, 1.537 mmol, 90%). The ee value of diol **24b** was 89%, was obtained by conversion of **24b** to the known[25] ketal and comparison of the reported optical rotations.

Diethyl [1-fluoro-3(*R*), 4-dihydroxybutyl]phosphonate 24b was obtained as above as a colorless liquid. $\delta_H(CDCl_3)$: 4.97-4.72 (m, 1H), 4.21-4.12 (m, 4H), 3.14-3.10 (m, 1H), 2.83 (t, J = 4.0 Hz, 0.5H), 2.75 (t, J = 4.0 Hz, 0.5H), 2.54 (m, 1H), 2.29-2.08 (m, 2H), 1.32 (m, 6H). $\delta_C(CDCl_3)$: 86.17 (dd, J = 180.2, 172. 6 Hz), 85.92 (dd, J = 180.9, 172.5 Hz), 63.35 (d, J = 3.1 Hz), 63.28 (d, J = 3.1 Hz), 63.00 (d, J = 4.6 Hz), 62.93 (d, J = 4.6 Hz), 48.49 (dd, J = 14.6, 3.8 Hz), 48.26 (dd, J = 17.6, 3.8 Hz), 47.63 (s), 46.41 (s), 37.80 (d, J = 19.8 Hz), 32.85 (d, J = 19.9 Hz), 16.40 (d, J = 12.4 Hz), 16.35 (d, J = 12.0 Hz). $\delta_F(CDCl_3)$: -207.73 (0.5F, m), -211.17 (0.5F, m). $\delta_P(CDCl_3)$: 19.91 (0.5P, d, J = 75.0 Hz), 19.40 (0.5P, d, J = 76.1 Hz). $[\alpha]^{20}_D$ = +16.30 (c = 4.50, MeOH).

Diethyl [1-difluoro-3(*R*)-3,4-epoxy-butyl]phosphonate 25b was recovered in resolved form as a colorless liquid. $\delta_H(CDCl_3)$: 4.97-4.72 (m, 1H), 4.21-4.12 (m, 4H), 3.14-3.10 (m, 1H), 2.83 (t, J = 4.0 Hz, 0.5H), 2.75 (t, J = 4.0 Hz, 0.5H), 2.54 (m, 1H), 2.29-2.08 (m, 2H), 1.32 (m, 6H). $\delta_C(CDCl_3)$: 85.92 (dd, J = 180.9, 172.5 Hz), 86.17

(dd, J = 180.2, 172. 6 Hz), 63.35 (d, J = 3.1 Hz), 63.28 (d, J = 3.1 Hz), 63.00 (d, J = 4.6 Hz), 62.93 (d, J = 4.6 Hz), 48.49 (dd, J = 14.6, 3.8 Hz), 48.26 (dd, J = 17.6, 3.8 Hz), 47.63 (s), 46.41 (s), 37.80 (d, J = 19.8 Hz), 32.85 (d, J = 19.9 Hz), 16.40 (d, J = 12.4 Hz), 16.35 (d, J = 12.0 Hz). $\delta_F(CDCl_3)$: -207.73 (0.5F, m), -211.17 (0.5F, m). $\delta_P(CDCl_3)$: 18.07 (d, J = 73.8 Hz). $[\alpha]^{20}_D$ = +12.06 (c = 2.33, MeOH).

Diethyl [1-fluoro-3(*S*)-hydroxyl-4-(oleoyloxy)butyl]phosphonate 26aa. To a solution of diol **24a** (107 mg, 0.438 mmol) and oleic acid (118 mg, 0.416 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DCC (109 mg, 0.526 mmol) and DMAP (32 mg, 0.263 mmol) in dry CH_2Cl_2 (1 mL) at 0°C. The solution was stirred for 16 h at 0 °C, filtered, concentrated in vacuo, and the residue was purified on silica gel (*n*-hexane-ethyl acetate, HE:AE = 1:1, R_f = 0.29) to afford ester 121 mg. (0.238 mmol, 51%) as a waxy solid. $\delta_H(CDCl_3)$: 5.29 (m, 2H), 5.10-4.89 (m, 1H), 4.22-3.98 (m, 7H), 3.48 (br, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.18-2.03 (m, 2H), 1.93 (m, 4H), 1.58 (m, 2H), 1.33-1.22 (m, 28H), 0.83 (t, J = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 173.84 (s), 173.81 (s), 129.92 (s), 129.64 (s), 86.49 (dd, J = 171.0, 172.6 Hz), 84.71 (dd, J = 171.1, 172.6 Hz), 68.06 (s), 67.48 (s), 66.01 (dd, J = 10.0, 3.8 Hz), 65.07 (dd, J = 13.1, 3.0 Hz), 63.55 (d, J = 6.9 Hz), 63.30 (d, J = 6.9 Hz), 63.06 (d, J = 6.9 Hz), 62.98 (d, J = 8.4 Hz), 34.36 (d, J = 19.9 Hz), 33.81 (d, J = 18.4 Hz), 31.82 (s), 29.67 (s), 29.61 (s), 29.43 (s), 29.23 (s), 29.09 (s), 27.13 (s), 27.08 (s), 24.86 (s), 22.59 (s), 16.35 (m), 14.02 (s). $\delta_F(CDCl_3)$: -208.26 (0.5F, m), -211.75 (0.5F, m). $\delta_P(CDCl_3)$: 19.36 (0.5P, d, J = 73.8 Hz), 19.10 (0.5P, d, J = 76.1 Hz). MS (CI) *m/z* 509.4 (M^++1, 29.75), 463.3 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 509.3400. Calcd for $C_{26}H_{51}FO_6P$, 509.3407. $[\alpha]^{20}_D$ = -2.61 (c = 2.38, MeOH).

Diethyl [1-fluoro-3(*S*)-hydroxyl-4-(palmitoyloxy)butyl]phosphonate 26ab was obtained similarly as a white solid, 51% yield. $\delta_H(CDCl_3)$: 5.11-4.90 (m, 1H), 4.23-3.99 (m, 7H), 3.42 (br, 1H), 2.31 (t, J = 7.6 Hz, 2H), 2.19-1.90 (m, 2H), 1.68-1.55 (m, 2H), 1.33 (t, J = 6.8 Hz, 6H), 1.60 (m, 24H), 0.84 (t, J = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 173.92 (s), 173.89 (s), 86.56 (dd, J = 171.0, 168.2 Hz), 84.78 (dd, J = 171.0, 168.2 Hz), 68.10 (s), 67.53 (s), 66.11 (dd, J = 9.3, 3.8 Hz), 65.21 (dd, J = 13.0, 3.1 Hz),

63.48 (dd, J = 24.6, 6.9 Hz), 63.05 (dd, J = 9.3, 6.8 Hz), 49.03 (s), 34.36 (d, J = 19.9 Hz), 31.87 (s), 29.63 (s), 29.60 (s), 29.41 (s), 29.22 (s), 29.09 (s), 25.59 (s), 24.86 (s), 22.63 (s), 16.41 (d, J = 5.3 Hz), 16.37 (d, J = 4.6 Hz), 14.06 (s). $\delta_F(CDCl_3)$: -208.37 (0.5F, m), -211.62 (0.5F, m). $\delta_P(CDCl_3)$: 19.34 (0.5P, d, J = 73.8 Hz), 19.11 (0.5P, d, J = 76.1 Hz). MS (CI) *m/z* 483.4 (M^++1, 55.29), 437.4 (M^+-OC_2H_5, 100.00). HRMS, M^++1, Found: 483.3244. Calcd for $C_{24}H_{49}FO_6P$, 483.3251. $[\alpha]^{20}_D$ = -2.20 (c = 1.00, MeOH).

[1-Fluoro-3(*S*)-hydroxyl-4-(oleoyloxy)butyl]phosphonate 3aa. Thoroughly dried precursor **26aa** (117 mg, 0.203 mmol, 5 h under high vacuum) was dissolved in dry methylene chloride (1 mL) at room temperature, and bromotrimethylsilane (353 mg, 2.030 mmol) was added with a dry syringe and the mixture was stirred for 4 h. When TLC indicated that all of the reactant had been consumed, the solvents were removed in vacuo. The residue was dissolved in 95% methanol (1 mL) for 1 h and reconcentrated in vacuo to give final product 88 mg (0.195 mmol, 96% yield) of phosphonate **3aa**. $\delta_H(CD_3OD)$: 5.34 (m, 2H), 5.21-5.17 (m, 1H), 4.79 (m, 1H), 3,68 (dd, J = 11.60, 4.40 Hz, 1H), 3.57 (m, 1H), 2.35 (m, 4H), 2.01 (m, 4H), 1.63 (m, 2H), 1.33-1.22 (m, 20H), 0.89 (t, J = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 174.33 (s), 174.17 (s), 130.84 (s), 130.74 (s), 88.16 (dd, J = 170.3, 168.7 Hz), 86.39 (dd, J = 170.3, 168.7 Hz), 71.30 (dd, J = 14.6, 2.3 Hz), 69.52 (dd, J = 14.6, 2.3 Hz), 35.12 (d, J = 19.3 Hz), 34.93 (d, J = 18.9 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). $\delta_F(CDCl_3)$: -208.60 (0.5F, m), -210.99 (0.5F, m). $\delta_P(CDCl_3)$: 16.21 (0.5P, d, J = 72.7 Hz), 15.95 (0.5P, d, J = 73.8 Hz). MS (CI) *m/z* 435.3 (M^+-OH, 60.85), 283.3 (M^+-C_4H_9-CFH_3PO_3, 100.00). HRMS, M^+-OH, Found: 435.2678. Calcd for $C_{22}H_{41}FO_5P$, 435.2676. $[\alpha]^{20}_D$ = -2.13 (c = 0.14, MeOH).

[1-Fluoro-3(*S*)-hydroxyl-4-(palmitoyloxy)butyl]phosphonate 3ab was obtained similarly from precursor **26ab** in 91% yield. $\delta_H(CD_3OD)$: 5.27-5.18 (m, 1H), 4.78 (m, 1H), 3,68 (dd, J = 10.80, 4.00 Hz, 1H), 3.57 (m, 1H), 2.40-2.25 (m, 4H), 1.64 (m, 2H), 1.33-1.22 (m, 24H), 0.89 (t, J = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 172.33 (s), 172.30 (s),

87.06 (dd, J = 170.3, 168.7 Hz), 85.29 (dd, J = 170.3, 168.7 Hz), 69.33 (dd, J = 14.2, 2.4 Hz), 67.56 (dd, J = 14.2, 2.4 Hz), 33.04 (d, J = 7.7 Hz), 31.92 (s), 31.06 (s), 28.77 (s), 28.75 (s), 28.71 (s), 28.58 (s), 28.47 (s), 28.39 (s), 28.15 (s), 24.05 (s), 23.97 (s), 23.92 (s), 21.72 (s), 12.48 (s). $\delta_F(CDCl_3)$: -208.73 (0.5F, m), -211.07 (0.5F, m). $\delta_P(CDCl_3)$: 16.21 (0.5P, d, J = 72.7 Hz), 15.95 (0.5P, d, J = 73.8 Hz). MS (CI) *m/z* 409.2 (M^++1-OH-CH_3, 2.29), 225.2 (M^+-$C_{14}H_{29}$-OH, 100.00). HRMS, M^+-OH-CH_3, Found: 408.2432. Calcd for $C_{20}H_{38}FO_5P$, 408.2441. $[\alpha]^{20}_D$ = -1.83 (c = 0.17, MeOH).

Diethyl [1-fluoro-3(*R*)-hydroxyl-4-(oleoyloxy)butyl]phosphonate 26ba was obtained as a waxy solid in 56% yield. $\delta_H(CDCl_3)$: 5.29 (m, 2H), 5.10-4.90 (m, 1H), 4.22-3.98 (m, 7H), 3.44 (br, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.18-2.03 (m, 2H), 1.93 (m, 4H), 1.56 (m, 2H), 1.33-1.22 (m, 28H), 0.83 (t, J = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 173.84 (s), 173.81 (s), 129.92 (s), 129.64 (s), 86.49 (dd, J = 171.0, 172.6 Hz), 84.71 (dd, J = 171.1, 172.6 Hz), 68.06 (s), 67.48 (s), 66.01 (dd, J = 10.0, 3.8 Hz), 65.07 (dd, J = 13.1, 3.0 Hz), 63.55 (d, J = 7.0 Hz), 63.30 (d, J = 7.0 Hz), 63.06 (d, J = 7.0 Hz), 62.98 (d, J = 8.4 Hz), 34.36 (d, J = 19.9 Hz), 33.81 (d, J = 18.4 Hz), 31.82 (s), 29.67 (s), 29.61 (s), 29.43 (s), 29.23 (s), 29.09 (s), 27.13 (s), 27.08 (s), 24.86 (s), 22.59 (s), 16.35 (m), 14.02 (s). $\delta_F(CDCl_3)$: -208.29 (0.5F, m), -211.75 (0.5F, m). $\delta_P(CDCl_3)$: 19.36 (0.5P, d, J = 73.8 Hz), 19.10 (0.5P, d, J = 76.1 Hz). $[\alpha]^{20}_D$ = +2.47 (c = 1.86, MeOH).

Diethyl [1-fluoro-3(*R*)-hydroxyl-4-(palmitoyloxy)butyl]phosphonate 26bb was obtained as a white solid in 53% yield. $\delta_H(CDCl_3)$: 5.11-4.90 (m, 1H), 4.20-3.99 (m, 7H), 3.42 (br, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.19-1.90 (m, 2H), 1.58 (t, J = 6.8 Hz, 2H), 1.33 (t, J = 6.8 Hz, 6H), 1.60 (m, 24H), 0.83 (t, J = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 173.88 (s), 173.85 (s), 86.00 (dd, J = 178.7, 171.1 Hz), 85.23 (dd, J = 178.7, 171.1 Hz), 68.06 (s), 67.50 (s), 66.05 (dd, J = 10.1, 4.6 Hz), 65.08 (dd, J = 10.1, 4.6 Hz), 63.44 (dd, J = 25.3, 7.6 Hz), 63.04 (dd, J = 6.8, 6.8 Hz), 34.37 (d, J = 19.9 Hz), 31.85 (s), 29.61 (s), 29.57 (s), 29.53 (s), 29.38 (s), 29.28 (s), 29.19 (s), 29.07 (s), 22.61 (s), 16.38 (d, J = 5.3 Hz), 16.34 (d, J = 4.6 Hz), 14.03 (s). $\delta_F(CDCl_3)$: -208.28 (0.5F, m), -211.75 (0.5F, m). $\delta_P(CDCl_3)$: 19.37 (0.5P, d, J = 73.8 Hz), 19.10 (0.5P, d, J = 76.1

Hz). $[\alpha]^{20}_D$ = +3.01 (c = 0.84, MeOH).

[1-Fluoro-3(*R*)-hydroxyl-4-(oleoyloxy)butyl]phosphonate 3ba was obtained in 94% yield from precursor **26ba**. $\delta_H(CD_3OD)$: 5.34 (m, 2H), 5.33-5.17 (m, 1H), 4.79 (m, 1H), 3,68 (dd, *J* = 11.60, 4.40 Hz, 1H), 3.59 (m, 1H), 2.35 (m, 4H), 2.02 (m, 4H), 1.61 (m, 2H), 1.33-1.22 (m, 20H), 0.89 (t, *J* = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 174.38 (s), 174.22 (s), 130.84 (s), 130.74 (s), 88.16 (dd, *J* = 170.25, 168.74 Hz), 86.39 (dd, *J* = 170.25, 168.74 Hz), 71.30 (dd, *J* = 14.58, 2.31 Hz), 69.52 (dd, *J* = *J* = 14.58, 2.31 Hz), 35.12 (d, *J* = 19.32 Hz), 34.93 (d, *J* = 18.89 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). $\delta_F(CDCl_3)$: -208.68 (0.5F, m), -210.99 (0.5F, m). $\delta_P(CDCl_3)$: 16.01 (0.5P, d, *J* = 72.86 Hz), 15.93 (0.5P, d, *J* = 74.00 Hz). $[\alpha]^{20}_D$ = +2.01 (c = 0.22, MeOH).

[1-Fluoro-3(*R*)-hydroxyl-4-(palmitoyloxy)butyl]phosphonate 3bb was obtained in 88% yield from precursor **26bb**. $\delta_H(CD_3OD)$: 5.27-5.18 (m, 1H), 4.78 (m, 1H), 3,68 (dd, *J* = 10.80, 4.00 Hz, 1H), 3.57 (m, 1H), 2.40-2.25 (m, 4H), 1.64 (m, 2H), 1.33-1.22 (m, 24H), 0.89 (t, *J* = 7.2 Hz, 3H). $\delta_C(CDCl_3)$: 172.33 (s), 172.30 (s), 87.06 (dd, *J* = 170.25, 168.74 Hz), 85.29 (dd, *J* = 170.25, 168.74 Hz), 69.33 (dd, *J* = 14.21, 2.35 Hz), 67.56 (dd, *J* = 14.21, 2.35 Hz), 33.04 (d, *J* = 7.68 Hz), 31.92 (s), 31.06 (s), 28.77 (s), 28.75 (s), 28.71 (s), 28.58 (s), 28.47 (s), 28.39 (s), 28.15 (s), 24.05 (s), 23.97 (s), 23.92 (s), 21.72 (s), 12.48 (s). $\delta_F(CDCl_3)$: -208.73 (0.5F, m), -211.07 (0.5F, m). $\delta_P(CDCl_3)$: 16.19 (0.5P, d, *J* = 72.70 Hz), 15.84 (0.5P, d, *J* = 73.84 Hz). $[\alpha]^{20}_D$ = +2.56 (c = 0.13, MeOH).

1-Diethylphosphonyl-3,4-*O*-isopropylidene-1(R,S),3(S),4-butanetriol 29. To a solution of diethyl phosphite (3.80 g, 24.07 mmol) in 8 mL of THF at -78°C, was added (24.07 mL) of 1.0M lithium bis(trimethylsilyl)amide in THF. The solution was allowed to r.t. and stirred for 45 min, and then cooled down to -20°C. Aldehyde **28** (3.3 g, 22.92 mmol) in 20 mL of THF was transferred into the solution at this temperature. The reaction mixture was allowed to warm to r.t. slowly and stirred fro overnight and then quenched by slow addition of acetic acid (24.1 mmol, 1.39 mL) in

10 mL of ether. It was filtered through Celite which was washed with ethyl acetate. The organic solvents were concentrated to give a colorless oil which was purified by flash chromatography to afford the phosphonate **29**.

1-Diethylphosphonyl-1-fluorine-3,4-*O*-isopropylidene-1(R,S),3(S),4-butanetriol 30 was prepared by DAST fluorination using the procedure described for compound **16**. $\delta_H(CDCl_3)$: 4.70-5.01 (m, 1H), 4.04-4.35 (m, 6H), 3.54-3.66 (m, 1H), 1.90-2.28 (m, 2H), 1.30-1.38 (m, 12H). $\delta_P(CDCl_3)$, 18.65 (d, J = 73.84 Hz, integration, 91.42), 18.36 (d, J = 76.10 Hz, integration, 8.58). $\delta_F(CDCl_3)$: -207.52 (0.085F, m), -212.52 (0.915F, m).

VI. Synthesis of Cyclic LPA Analogs

General procedures. Chemicals were obtained from Aldrich and Arcos Chemical Corporation and were used without prior purification. Solvents used were of reagent grade and were distilled before use: THF was distillated from sodium wire. Methylene chloride was distillated from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. ^1H and ^{13}C spectra were recorded at 400 MHz (^1H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F), temp. 25°C. Chemical shifts are given in ppm with TMS as internal standard (δ = 0.00); ^{31}P, 85% H_3PO_4 (δ = 0.00); ^{19}F, $CFCl_3$ (δ = 0.00). Figures 17, 21 and 22 provide reaction schemes for producing the cyclic compounds described below. Figures 18-20 provide proposed reactions schemes for producing cyclic compounds described herein.

(*E*)-(3*R*)-Diethyl 1-Fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-enylphosphonate 2. Treatment of tetraethyl fluoromethylenebisphosphonate (0.184 mg, 0.601 mmol in 5 mL dry hexane) with n-BuLi (0.601 mL, 1.0 M solution in hexane) at -78°C under dry nitrogen gas followed by addition of (*R*)-1,4-dioxaspiro[4,5]decane-2-carbaldehyde (0.143 g, 0.841 mmol) with stirring at -78°C gave a mixture which was brought to room temperature slowly. Filtration and evaporation under reduced temperature, followed by chromatography (ethyl acetate/hexane: 3/2) gave two isomers **2** (R_f = 0.19, 0.178 g, 0.553 mmol, 92%). ^1H NMR($CDCl_3$): 5.99 (dt, J = 39.2, 7.6 Hz,1H), 4.98 (m, 1H), 4.17-4.08 (m, 5H), 3.63

(dd, J = 7.6, 6.4 Hz, 1H), 1.56 (m, 10H), 1.32 (m, 6H). ^{13}C NMR($CDCl_3$): 151.85 (dd, J = 278.0, 233.2 Hz), 124.36 (dd, J = 27.6, 3.0 Hz), 110.6 (s), 68.67 (dd, J = 12.3, 6.9 Hz), 68.45 (m), 63.29 (dd, J = 5.3, 3.0 Hz), 36.09 (s), 35.17 (s), 24.97 (s), 23.78 (s), 16.17 (d, J = 6.1 Hz). ^{19}F NMR($CDCl_3$): -127.04 (dd, J = 99.0, 39.1 Hz, 1F). ^{31}P NMR($CDCl_3$): 4.68 (d, J = 98.9 Hz). MS (CI) m/z 323 (M^++1, 69.89), 99 ($OC_6H_{11}^+$, 100.00). HRMS, M^+, Found: 322.1354. Calcd for $C_{14}H_{24}FO_5P$, 322.1345. $[\alpha]^{20}_D$ = +51.68 (c = 0.15, EtOH).

(3*R*)-Diethyl 1-fluoro-3,4-*O*-cyclohexylidene-3,4-dihydroxybut-1-phosphonate (3). A solution of **2** (0.128 g, 0.398 mmol) in absolute ethanol (8 mL) containing 10% Pd-C catalyst (10 mg) was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration and evaporation under reduced pressure gave compound **3** as a colourless liquid (0.126 g, 0.390 mmol, 98% yield). ^{1}H NMR ($CDCl_3$): 4.99-4.76 (m, 1H), 4.33-4.01 (m, 5H), 3.63-3.54 (m, 1H), 2.25-1.98 (m, 2H), 1.56 (m, 8H), 1.31 (m, 8H). ^{13}C NMR ($CDCl_3$): 109.70 (s), 109.66 (s), 86.14 (dd, J = 179.4, 171.8 Hz), 86.00 (dd, J = 179.4, 171.8 Hz), 71.92 (dd, J = 11.5, 3.0 Hz), 71.27 (dd, J = 11.5, 3.0 Hz), 68.94 (s), 68.33 (s), 63.09 (dd, J = 39.9, 6.9 Hz), 62.98 (dd, J = 33.7, 4.6 Hz), 36.70 (s), 36.1417 (s), 35.06 (s), 34.81 (s), 33.99 (d, J = 19.1 Hz), 16.40 (d, J = 6.1 Hz). ^{19}F NMR ($CDCl_3$): -207.52 (m), -212.53 (m). ^{31}P NMR ($CDCl_3$): 18.76 (d, J = 73.8 Hz), 18.47 (d, J = 73.8 Hz). MS (CI) m/z 325 (M^++1, 100.00). HRMS, M^+, Found: 324.1519. Calcd for $C_{14}H_{26}FO_5P$, 324.1502. $[\alpha]^{20}_D$ = -5.59 (c = 0.34, EtOH).

(3*R*)-Diethyl 1-fluoro-3,4-dihydroxybutane-1-phosphonate (4). TsOH (7 mg, 0.035 mmol, 0.10 eq.) was added to a solution of **3** (0.114 g, 0.352 mmol) in MeOH (5 mL), and the solution was stirred at room temperature for 24 h. After addition of solid $NaHCO_3$ to neutralize the reaction mixture, the solvent was removed under reduced pressure. Chromatography afforded the homogenous product **4** (75 mg, 0.306 mmol, 87%). ^{1}H NMR ($CDCl_3$): 5.11-4.87 (m, 1H), 4.19-4.08 (m, 5H), 3.96 (br, 1H), 3.79 (br, 1H), 3.59 (m, 1H), 3.40 (m, 1H), 2.15-1.77 (m, 2H), 1.30 (t, J = 6.8 Hz, 8H).

^{19}F NMR ($CDCl_3$): -207.43 (m), -211.70 (m). ^{31}P NMR ($CDCl_3$): 19.89 (d, J = 74.0 Hz), 19.36 (d, J = 75.9 Hz). $[\alpha]^{20}_D$ = -13.42 (c = 0.73, EtOH).

1-Fluoro-3 (S),4-dihydroxylbutane-phosphonate (5). A thoroughly dried sample of 4 (46 mg, 0.189 mmol, 5 h under high vacuum) was dissolved in anhydrous methylene chloride (1 mL) at room temperature. Bromotrimethylsilane (0.25 mL, 1.890 mmol) was added with a dry syringe and stirred 4 h. TLC indicated that all of the reactant had disappeared, then the solvent was removed under reduced pressure and the residue was dried under vacuum. The residue was then dissolved in 95% methanol (1 mL) for 1 h, and the solvent was removed under reduced pressure and the product dried under vacuum, to give 33 mg (0.176 mmol, 93% yield) of diol 5. ^1H NMR (CD_3OD): 4.90 (m, 1H), 3.92-3.79 (m, 1H), 3.50 (m, 2H), 2.15 (m, 2H), 3.57 (m, 1H). ^{13}C NMR (CD_3OD): 88.16 (dd, J = 170.3, 168.7 Hz), 86.39 (dd, J = 170.3, 168.7 Hz), 70.10 (dd, J = 8.4, 2.3 Hz), 68.41 (dd, J = 13.1, 2.3 Hz), 67.48 (s), 66.64 (s), 35.30 (m). ^{19}F NMR (CD_3OD): -207.35 (1F, m), -212.58 (1F, m). ^{31}P NMR (CD_3OD): 18.00 (d, J = 75.0 Hz), 17.57 (d, J = 76.1 Hz).

1-Fluoro-3(S)-hydroxyl-4-oxyoleoylbutane-1,2-cyclic phosphonate (7). 1.0 M dicyclohexylcarbodiimide in methylene chloride solution (1.4 eq., 0.216 mL, 0.216 mmol) was added dropwise to diol 5 (29 mg, 0.154 mmol) in 50 mL of anhydrous DMF solution. After 12 h, the cyclization reaction was complete and compound 6 was formed. Several drops of water were added to quench the reaction. After removing the solvent, the crude residue containing 6 was dissolved in anhydrous pyridine (2 mL). To the pyridine solution was added oleyl chloride (1.4 eq., 0.084 mL, 0.216 mmol) with vigorous stirring. After stirring for 12 h at room temperature, the solvent was removed and the crude CHF-ccLPA product was then purified on a Sephadex LH-20 column, eluting with CH_2Cl_2 : CH_3OH = (7:3). Appropriate fractions were collected (R_f = 0.39, CH_2Cl_2 : CH_3OH : H_2O = 65 : 25 : 4, 43 mg, 0.100 mmol, 65%). The product was dissolved in 1.0 M triethylammonium bicarbonate (TEAB) buffer (pH 8.0) to give a slightly cloudy solution, which was absorbed onto a sodium ion-exchange column (Dowex 50WX8-200 resin, neutral Na^+ form). The desired mixed

neutral sodium salt of **7** was eluted with Nanopure water. The product solution was lyophilized to give an amorphous white powder, which was stored in solid form at -80 °C under nitrogen atmosphere. ^{1}H NMR (CD_3OD /D_2O): 5.33 (m, 2H), 5.10-5.00 (m, 1H), 4.49-4.38 (m, 1H), 4.24-4.10 (m, 2H), 2.37 (m, 2H), 2.15 (m, 2H), 2.00 (m, 4H), 1.59 (m, 2H), 1.26 (m, 20H), 0.89 (t, J = 7.2 Hz, 3H). ^{19}F NMR (CD_3OD /D_2O): -197.97 (1F, m), -203.30 (1F, m). ^{31}P NMR (CD_3OD /D_2O): 32.28 (d, J = 65.0 Hz), 31.82 (d, J = 67.4 Hz).

Dimethyl 4-(benzyloxy)-3-hydroxybutanephosphonate (9) (Figure 21). A 2.5 M solution of n-BuLi (60 mL, 150 mmol) in hexane was added dropwise to a stirred solution of methylphosphonate (18.6 g, 16.25 mL, 150 mmol) in dry THF (150 mL) at -78 °C under a nitrogen atmosphere. After 15 min of stirring, a solution of the benzyl glycidol ether (**8**) (8.21 g, 7.65 mL, 50 mmol) in THF (25 mL) was added dropwise, followed by $BF_3{\cdot}OEt_2$ (25.35 mL, 200 mmol), which was slowly introduced while maintaining the temperature below -70 °C. After the solution was stirred for two more hours, the reaction was quenched with saturated NH_4Cl (150 mL) and was allowed to warm up to room temperature. The residue obtained after evaporation under reduced pressure was extracted with ethyl acetate (200 mL×4). The solution was washed with brine, dried with Na_2SO_4, and concentrated, and the residue was chromatographed (Acetone/hexane: 1/1, R_f = 0.30) on silica gel to yield the pure hydroxy phosphonate ester. (14.8 g, 51.3 mmol, 100%). ^{1}H NMR($CDCl_3$): 7.30-7.22 (m, 5H), 4.48 (s, 2H), 4.34 (m, 1H), 3.76 (d, J = 10.8 Hz, 6H), 3.39 (m, 2H), 2.23 (m, 1H), 2.09 (m, 1H), 1.96 (m, 1H), 1.85 (m, 1H). ^{31}P NMR($CDCl_3$): 36.60 (s). MS (CI) m/z 289.1 (M^++1, 100.00). HRMS, M^++1, Found: 289.1211. Calcd for $C_{13}H_{22}O_5P$, 289.1217.

Methyl 3-hydroxyl-4-benzylbutane-1,3-cyclic phosphonate (10). Dimethyl 4-(benzyloxy)-3-hydroxybutanephosphonate (16.0 g, 70.18 mmol) was dissolved in anhydrous toluene (450 mL) and PPTS (pyridinium p-toluene sulfonate, 34.0 g, 140 mmol) was added. The mixture is heated to 80 °C for 20 hours. After cooled to room

temperature, H_2O (200 mL) was added, and the solution was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4, and concentrated, and the residue was chromatographed (Acetone/hexane: 1/1, $R_f = 0.48$) on silica gel to yield the pure hydroxy phosphonate ester. (7.97 g, 31.13 mmol, 44%). ^1H NMR($CDCl_3$): 7.33-7.26 (m, 5H), 4.57 (s, 2H), 4.34 (m, 1H), 3.76 (d, $J = 10.8$ Hz, 3H), 3.56 (m, 2H), 2.23 (m, 1H), 2.09 (m, 1H), 1.96 (m, 1H), 1.85 (m, 1H). ^{13}C NMR($CDCl_3$): 137.60 (s), 128.36 (s), 127.71 (s), 127.67 (s), 127.52 (s), 77.29 (d, J = 9.96 Hz), 73.53 (s), 72.06 (d, $J =$ 6.13 Hz), 52.39 (d, $J = 6.93$ Hz), 25.82 (s), 18.26 (d, $J = 121.17$ Hz). ^{31}P NMR($CDCl_3$): 51.04 (s). MS (CI) m/z 257.1 (M^++1, 100.00). HRMS, M^+, Found: 257.0980. Calcd for $C_{12}H_{18}O_4P$, 257.1017.

Methyl 3,4-dihydroxybutane-1,3-cyclic phosphonate (11). A solution of **10** (2.1 g, 8.203 mmol) in absolute methanol (100 mL) containing 10% Pd-C catalyst (0.83 g) was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration and evaporation under reduced pressure gave compound **11**, which was purified on silica gel (1.06 g, 6.40 mmol, 78% yield). ^1H NMR ($CDCl_3$): 4.27 (m, 1H), 3.68-3.76 (m, 1H), 3.72 (d, $J = 12.0$ Hz), 3.60 (m, 1H), 2.10-2.22 (m, 2H), 2.00 (m, 1H), 1.80 (m, 1H). ^{13}C NMR ($CDCl_3$): 79.31 (d, $J = 10.0$ Hz), 64.49 (d, $J =$ 6.1 Hz), 52.50 (d, J = 6.9 Hz), 24.89 (s), 18.47 (d, $J = 120.65$ Hz).. ^{31}P NMR ($CDCl_3$): 52.11 (s). MS (CI) m/z 167.0 (M^++1, 100.00). HRMS, M^+, Found: 167.0474. Calcd for $C_5H_{12}O_4P$, 167.0475.

Methyl 3-hydroxyl-4-*terta*-Butyldimethylsilylbutane-1,3-cyclic phosphonate (12). Alcohol **11** (0.420g, 2.53 mmol) was dissolved in anhydrous DMF (10 mL) and stirred with imidazole (0.206 g, 3.04 mmol, 1.2 equiv) and *tert*-butyldimethylsilyl chloride (TBSCl) (0.420 g, 2.78mmol, 1.1 equiv) for 24 h at room temperature. The solution was diluted with water (5 mL) and ethyl acetate (20 mL), and the aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo, and the residue was purified on silica gel (hexanes-ethyl acetate 2:1, $R_f = 0.40$) to afford TBDMS ether **12** as a colorless liquid 0.392 g (1.324 mmol, 67%). ^1H NMR (CD_3Cl): 4.22 (m, 1H),

3.76-3.71 (m, 5H), 2.24-2.06 (m, 2H), 1.97-1.74 (m, 2H), 0.84 (s, 9H), 0.02 (m, 6H). ^{13}C NMR (CD_3Cl): 78.19 (d, J = 9.2 Hz), 67.17 (d, J = 6.1 Hz), 52.14 (d, J = 6.9 Hz), 25.63 (s), 25.46 (d, J = 23.0 Hz), 18.67 (d, J = 122.68 Hz). 18.08 (s). -5.61 (s), -5.67 (s). MS (CI) m/z 281.2 (M^++1, 100.00). HRMS, M^++1, Found: 281.1342. Calcd for $C_{11}H_{26}O_4PSi$, 281.1346.

Methyl 3-hydroxyl-4-*terta*-Butyldimethylsilylbutane-1,3-cyclic thiophosphonate (13). A solution of **12** (0.553 g, 1.975 mmol) and Lawesson's Reagent (0.44 g, 1.086 mmol) in toluene (3 mL) was stirred and heated at reflux for 4 h. The reaction mixture was washed with water (3 mL) and extracted with toluene (3 × 3 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, the solvent was removed in vacuum, and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane, 1:10, R_f = 0.30) to give **13** (0.392 g, 67% yield) as a colorless liquid. ^1H NMR (CD_3Cl): 4.37 (m, 1H), 3.67-3.71 (m, 5H), 2.12-2.32 (m, 4H), 0.85 (s, 9H), -0.05 (s, 6H). ^{13}C NMR (CD_3Cl): 81.52 (d, J = 3.9 Hz), 65.38 (d, J = 6.8 Hz), 52.35 (d, J = 6.9 Hz), 29.21 (d, J = 84.46 Hz), 25.72 (s), -0.08 (s), -5.36 (s), -5.55 (s). ^{31}P NMR (CD_3Cl): 113.43 (s). MS (CI) m/z 297.1 (M^++1, 100.00). HRMS, M^++1, Found: 297.1128. Calcd for $C_{11}H_{26}O_3PSSi$, 297.1146.

Methyl 3,4-dihydroxyl-butane-1,3-cyclic thiophosphonate (14). A solution of **13** (143 mg, 0.483 mmol) in THF (8 mL) was treated consecutively with acetic acid (83 μL, 1.449 mmol) and tetrabutylammoniumfluoride trihydrate (457 mg, 1.449 mmol) at room temperature. After the solution was stirred for 18 h the reaction was complete (TLC control), the solvent was then evaporated under reduced pressure and the crude product was purified on a short column of silica gel (acetone/hexane, 3:2, R_f = 0.45) to afford a colorless liquid.(61 mg, 0.335 mmol, 69% yield.). ^1H NMR (CD_3Cl): 4.30 (m, 1H), 3.55-3.76 (m, 5H), 2.92 (m, 1H), 2.02-2.31 (m, 5H). ^{13}C NMR (CD_3Cl): 82.21 (d, J = 3.8 Hz), 64.49 (d, J = 6.1 Hz), 52.52 (d, J = 6.8 Hz), 29.53 (d, J = 92.49 Hz), 25.39 (s). ^{31}P NMR (CD_3Cl): 113.99 (s). MS (CI) m/z 183.0 (M^++1, 100.00). HRMS, M^++1, Found: 183.0245. Calcd for $C_5H_{12}O_3PS$, 183.0246.

Methyl 3-hydroxyl-4-oleylbutane-1,3-cyclic thiophosphonate (15). To a pyridine solution (3 mL) of **14** (47 mg, 0.258 mmol) was added oleyl chloride (1.4 eq., 0.14 mL, 0.362 mmol) with good stirring. After being stirred at room temperature for 12 h, the solvent was removed and the crude product was then purified on silica gel (Ethyl acetate/hexane, 1:2, R_f= 0.40) to afford a colorless liquid (99 mg, 0.222 mmol, 86% yield.). ^{1}H NMR (CD_3Cl): 5.29 (m, 2H), 4.42 (m, 1H), 4.26 (m, 1H), 4.07 (m, 1H), 3.72 (d, J= 12.0 Hz, 3H), 1.60-2.35 (m, 13H), 1.23-1.27 (m, 22H), 0.85 (t, J= 6.9 Hz, 3H). ^{13}C NMR (CD_3Cl): 173.50 (s), 129.99 (s), 129.70 (s), 78.72 (d, J= 10.7 Hz), 65.42 (d, J= 6.9 Hz), 52.61 (d, J= 6.9 Hz), 34.00 (s), 33.36 (s), 31.87 (s), 29.73 (s), 29.66 (s), 29.49(s), 29.29 (s), 29.12 (s), 29.06 (s), 27.19 (s), 27.13 (s), 25.72 (s), 24.78 (s), 22.65 (s), 19.08 (s), 17.87 (s), 14.09 (s). ^{31}P NMR (CD_3Cl): 112.96 (s). MS (CI) m/z 447.1 (M^++1, 100.00). HRMS, M^++1, Found: 447.2632. Calcd for $C_{23}H_{43}O_4PS$, 447.2648.

3-hydroxyl-4-oleylbutane-1,3-cyclic thiophosphonate (16). A solution of **15** (18 mg, 0.004 mmol) in 3 mL of *tert*-butylamine was refluxed for 48 h. Excess *tert*-butylamine was removed by evaporation and the resulting residue was purified on silica gel (CH_2Cl_2/CH_3OH/H_2O, 8:1:0.05, R_f= 0.14) to afford a colorless liquid.(14 mg, 0.003 mmol, 75% yield.) The labile acid forms of these analogues were then converted to neutral sodium salts **17**. Thus, product **16** was dissolved in 2 mL of 1.0 M triethylammonium bicarbonate (TEAB) buffer (pH 8.0) to give a slightly cloudy solution, which was absorbed to a sodium ion-exchange column (Dowex 50WX8-200 resin, neutral Na^+ form). The desired mixed neutral sodium salt **17** was eluted with Nanopure water. The product solution was lyophilized to give sodium salt as white amorphous solid, which was stored in solid form at -80 °C under nitrogen atmosphere. The cyclic carbon PA analogue **19** (Figure 22) was converted to the corresponding sodium salts in the same procedure. ^{1}H NMR of **16** (CD_3OD): 5.34 (m, 2H), 4.44 (m, 1H), 4.20 (dd, J= 12.0, 3.2 Hz, 1H), 4.09 (dd, J= 11.6, 6.0 Hz, 1H), 2.35 (t, J= 8.0 Hz, 2H), 2.10-2.20 (m, 2H), 2.02 (m, 6H), 1.61 (m, 2H), 1.31 (m, 22H), 0.89 (t, J= 6.9 Hz, 3H). ^{13}C NMR (CD_3OD): 173.23 (s), 128.88 (s), 128.82 (s),

75.98 (s), 65.63 (s), 32.95 (s), 31.08 (s), 28.85 (s), 28.81 (s), 28.62 (s), 28.46(s), 28.34 (s), 28.30 (s), 28.21 (s), 26.13 (s), 23.97 (s), 21.75 (s), 12.47 (s). ^{31}P NMR (CD_3OD): 93.88 (s). MS (CI) m/z 433.3 (M^++1, 100.00). HRMS, M^++1, Found: 433.2544. Calcd for $C_{22}H_{41}O_4PS$, 433.2547.

Methyl 3-hydroxyl-4-oleylbutane-1,3-cyclic phosphonate (18) (Figure 22). To a solution of alcohol **11** (58 mg, 0.349 mmol) and oleic acid (108 mg, 0.419 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DCC (86 mg, 0.419 mmol) and DMAP (26 mg, 0.209 mmol) in dry CH_2Cl_2 (2 mL) at room temperature. The solution was stirred for 16 h at room temperature, filtered, concentrated in vacuo, and the residue was purified on silica gel (*n*-hexane-ethyl acetate, HE:AE = 1:3, R_f= 0.25) to afford ester **18** (87 mg, 0.202 mmol, 58%) as a liquid. ^{1}H NMR (CD_3Cl): 5.91 (m, 2H), 4.38 (m, 1H), 4.09 (ABd, *J* = 12.0, 6.0 Hz, 1H), 4.26 (AB, *J* = 12.0 Hz, 1H), 3.77 (d, *J* = 12.0 Hz, 3H), 1.60-2.35 (m, 13H), 1.23-1.27 (m, 22H), 0.85 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (CD_3Cl): 173.46 (s), 129.99 (s), 129.70 (s), 75.67 (d, J = 10.7 Hz), 65.56 (d, J = 6.9 Hz), 52.54 (d, J = 6.9 Hz), 34.00 (s), 33.36 (s), 31.87 (s), 29.73 (s), 29.66 (s), 29.49(s), 29.29 (s), 29.12 (s), 29.06 (s), 27.19 (s), 27.13 (s), 25.72 (s), 24.78 (s), 22.65 (s), 18.48 (d, *J* = 121.68 Hz), 14.09 (s). ^{31}P NMR (CD_3Cl): 54.01 (s). MS (CI) m/z 431.4 (M^++1, 100.00). HRMS, M^++1, Found: 431.2929. Calcd for $C_{23}H_{43}O_5P$, 431.2931.

3-Hydroxyl-4-oleylbutane-1,3-cyclic phosphonate (19). Thoroughly dried precursor **18** (56 mg, 0.130 mmol, 5 h under high vacuum) was dissolved in dry methylene chloride (0.5 mL) at room temperature, and bromotrimethylsilane (70 mg, 0.456 mmol) was added with a dry syringe and the mixture was stirred for 1 h. When TLC indicated that all of the reactant had been consumed, the solvents were removed in vacuo. The residue was dissolved in 95% methanol (1 mL) for 1 h and reconcentrated in vacuo to give final product 51 mg (0.123 mmol, 94% yield) of phosphonate **19**. ^{1}H NMR (CD_3OD): 5.34 (m, 2H), 4.50 (m, 1H), 4.27 (dd, *J* = 12.0, 3.2 Hz, 1H), 4.10 (dd, *J* = 11.6, 6.0 Hz, 1H), 2.35 (t, *J* = 8.0 Hz, 2H), 2.10-1.80 (m, 8H), 1.62 (m, 2H), 1.31 (m, 22H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (CD_3OD):

173.67 (s), 129.73 (s), 129.63 (s), 76.53 (dd, J = 12.0 Hz), 65.72 (dd, J = 5.3 Hz), 33.67 (s), 31.94 (s), 29.73 (s), 29.67 (s), 29.44 (s), 29.34 (s), 29.22 (s), 29.17 (s), 29.07 (s), 29.05 (s), 27.01 (s), 25.08 (s), 24.79 (s), 22.61 (s), 19.29 (d, J = 120.67 Hz), 13.38 (s). MS (CI) m/z 417.0 (M^++1, 40.31), 135.0 (M^+-RCO_2, 100.00). HRMS, M^++1, Found: 417.2772. Calcd for $C_{22}H_{41}O_5P$, 417.2774.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the compounds, compositions and methods described herein.

Various modifications and variations can be made to the compounds, compositions and methods described herein. Other aspects of the compounds, compositions and methods described herein will be apparent from consideration of the specification and practice of the compounds, compositions and methods disclosed herein. It is intended that the specification and examples be considered as exemplary.

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